CORE-MD

Coordinating Research and Evidence for Medical Devices

Report on study design recommendations in guidance documents for high-risk medical devices

Deliverable 1.6

Deliverable factsheet

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Acronyms and abbreviations

AAA	Abdominal Aortic Aneurysm
ADE	Adverse Device Effect
AE	Adverse Event
AER	Adverse Event Reporting
AETSA	Fundación Pública Andaluza Progreso y Salud – Andalusian Health Technology Assessment Unit
AICDs	Active implantable cardiac devices
AIMDD	Active Implantable Medical Devices Directive
AOANJRR	Australian Orthopedic Association National Joint Replacement Registry
ARC	Academic Research Consortium
ASADE	Anticipated Serious Adverse Device Effect
BUH	Insel Gruppe AG - Bern University Hospital
CDRH	Center for Devices and Radiological Health (FDA)
CEAR	Clinical Evaluation Assessment Report
CEN	European Committee for Standardization
CENELEC	European Committee for Electrotechnical Standardization
CEP	Clinical Evaluation Plan
CER	Clinical Evaluation Report
CFR	Code of Federal Regulations (USA)
CHF	Schweizer Franken
CI	Clinical Investigation(s)
CIC	Clinical Investigation Chapter
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CONSORT	Consolidated Standards of Reporting Trials
CORE-MD	Coordinating Research and Evidence for Medical Devices
CPR	Cumulative Percentage Revision
CRFs	Case Report Forms
CS	Common Specifications

CTTI	Clinical Trials Transformation Initiative
DH	Declaration of Helsinki
DMC	Data Monitoring Committee
DS	Device-specific
EC	European Commission
EEM	External Evidence Methods
EFFORT	European Federation of National Associations of Orthopedics and Traumatology
EHR	Electronic Health Record
EQUATOR network	Enhancing the QUAlity and Transparency Of health Research
ER	Essential Requirements
ESC	European Society of Cardiology
ESOs	European Standardization Organizations
EU	European Union
EU MDD	European Medical Device Directives
EU MDR	European Medical Device Regulation
EUDAMED	EU database for medical devices
FAMHP	Belgium Federal Agency for Medicines and Health Products
FDA	U.S. Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force on Medical Devices
GMDN	Global Medical Device Nomenclature
GSPR	General Safety and Performance Requirements
HMEs	Heat and Moisture Exchangers
HPRA	Health Products Regulatory Authority
HTA	Health Technology Assessment
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
iCRNs	international Coordinated Registry Networks
IEC	International Electrotechnical Commission
IFU	Instructions for use

IMDRF	International Medical Device Regulators Forum
IRB	Institutional Review Boards
ISO	International Organization for Standardization
ITT	Intention-to-treat
IVD	In vitro diagnostics
IVDDs	In vitro diagnostic devices
LUMC	Leiden University Medical Center
MCID	Minimally clinically important differences
MD	Medical Devices
MDCG	Medical Device Coordination Group (of the European Union)
MDD	Medical Device Directives
MDIC	Medical Device Innovation Consortium
MDR	Medical Device Regulation
MEDDEV	Medical Device Directives (guidance documents)
MHRA	United Kingdom Medicines & Healthcare Products Regulatory Agency
MISS	Missing values
MoH	Ministry of Health – Italy
MP	Medizinprodukte German for medical devices
MPAMIV	Medizinprodukte-Anwendermelde- und Informationsverordnung
MPDG	Medizinproduktedurchführungsgesetz
NB	Notified body
NESTcc	National Evaluation System for Health Technology Coordination Center
NHMRC	National Health and Medical Research Council in Australia
OJEU	Official Journal of the European Union
OPC	Objective performance criteria
OPG	Objective performance goal
PDA	Patent ductus arteriosus
PEAC	Patient Engagement Advisory Committee (FDA)
PG	Performance Goal(s)
PICO	Population, Intervention, Comparator, Outcomes

PMA	Pre-market Approval (FDA)
PMCF	Post Market Clinical Follow-up
PMDA	Pharmaceuticals and Medical Device Agency of the Ministry of Health, Labour and Welfare (Japan)
PMS	Post-market surveillance
PP	Per-protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PROMs	Patient reported outcome measures
PS	Pre-specification
QoL	Quality of life
RCT	Randomized controlled trial
RWD	Real world data
RWE	Real world evidence
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Study protocol
SS	Sample Size calculation
SSCP	Summary of Safety and Clinical Performance
SSED	Summary of Safety and Effectiveness Data
SSR	Sample size reassessment
STARD	Standard for Reporting Diagnostic Accuracy Studies
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Team-NB	The European Association for Medical Devices of Notified Bodies
TGA	Department of Health, Therapeutic Goods Administration (Australia)
TPD	Health Canada Medical Devices Bureau of the Therapeutic Products Directorate
UDI	Unique Device Identifier
UK	United Kingdom

UMIT TIROL	UMIT TIROL - University for Health Sciences and Technology
USADE	Unanticipated serious adverse device effect
VARC	Valve Academic Research Consortium
VDDCP	Vascular device-drug combination product
WET	Well-established technologies
WG	Working group
WP	Work package(s)

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Abstract

Objectives

The objectives of this report were to identify guidance documents concerning clinical investigations of high-risk medical devices, describe their contents and compare their principal recommendations for designing, analyzing, and reporting clinical studies, with a focus on methodologies for confirmatory pivotal trials. This report is intended as a reference summary for healthcare professionals and health technology developers. A secondary objective is to identify gaps in regulatory guidance, and therefore topics for research on trial methodologies in the context of approval processes.

Methods

A study protocol was developed and registered in the Open Science Framework on January 20th, 2022. We included guidance documents on high-risk therapeutic medical devices such as implants (class IIb and III according to the MDR). General guidance documents for high-risk devices or broader definitions that cover high-risk devices have been included. With regard to device-specific guidance, we included guidance documents relating to cardiovascular and orthopedic high-risk devices, and high-risk devices for diabetes.

We included guidance documents from regulatory authorities of high-income countries, the International Organization for Standardization (ISO), the International Medical Device Regulators Forum (IMDRF), and from regulatory-private research consortia since 2000.

Results

A total of 30 regulatory guidance documents are reviewed in detail, including 19 from six national jurisdictions [Belgium 1, United Kingdom 3, Australia 2, Canada 1, Japan 1, United States of America 11]; eight from the EU; and three from the IMDRF (Table 28; and section 4.4Table 29Table 29). Twelve ISO standards are also reviewed (Table 3; and section 4.3), including three general standards relating to clinical investigations and risk management and nine specific standards relating to cardiovascular devices. No ISO standards covering clinical investigations for orthopedic high-risk devices or high-risk devices for diabetes have been identified. Finally, four documents from regulatory-private research consortia were included (Table 6; and section 4.5).

There is detailed and systematic guidance on study design of high-risk medical devices from regulators available regarding level of evidence, need for a clinical investigation, choice of study design, general design issues and Population - Intervention – Comparator – Outcome scheme (PICO), and statistical methods, but this guidance comes mainly from the U. S. Food and Drug Administration (FDA). In addition, guidance from the Medical Device Coordination Group (MDCG) so far is predominantly limited to reporting templates, only the MEDDEV 2.7/1. revision 4 guidance document still issued under the Medical Device Directives contains more substance matter guidance on trials design, but from the viewpoint of clinical evaluation. The guidance documents differ considerably in the degree to which the methodology of study design is treated in a systematic and comprehensive manner.

Gaps identified in trials methodology for confirmatory studies are a clarifying terminology of "objective performance criterion" over different legislations, and a methodology to validly derive performance criteria. Since the degree of maturity of a technology seems to be an important factor to guide the appropriate study design, criteria to distinguish more clearly between well-established and new technologies would be helpful.

Conclusions

For a better predictability what is considered appropriate study design under the Medical Device Regulation development of guidance for trial design by the MDCG is still needed.

For device-specific guidance on study design, whether from regulators or the International Organization for Standardization, a transparent, scientifically valid, and standardized methodology should be applied to collect and assess the current state of science on device-specific design issues.

In order to identify practically relevant research gaps in the study design of confirmatory studies, the experience of the notified bodies and expert panels providing an opinion on the evidence in the clinical evaluation assessment reports should be used.

Executive Summary

Objectives

The objectives of this report were to identify guidance documents concerning clinical investigations of high-risk medical devices, describe their contents and compare their principal recommendations for designing, analyzing, and reporting clinical studies, with a focus on methodologies for confirmatory pivotal trials. This report is intended as a reference summary for healthcare professionals and health technology developers. A secondary objective is to identify gaps in regulatory guidance, and therefore topics for research on trial methodologies in the context of approval processes.

Methods

A study protocol was developed and registered in the Open Science Framework on January 20th, 2022. We included guidance documents on high-risk therapeutic medical devices such as implants (class IIb and III according to the MDR). General guidance documents for high-risk devices or broader definitions that cover high-risk devices have been included. With regard to device-specific guidance, we included guidance documents relating to cardiovascular and orthopedic high-risk devices, and high-risk devices for diabetes.

We included guidance documents from regulatory authorities of high-income countries, the International Organization for Standardization (ISO), the International Medical Device Regulators Forum (IMDRF), umbrella organizations of notified bodies in Europe and from regulatory-private research consortia since 2000.

We searched the websites of ISO, international and national regulatory organizations and public-private research consortia, and umbrella organizations of notified bodies in Europe, between May 2021 and February 2022. We checked whether documents have been updated until December 2022.

Documents from the internet search were screened and downloaded by one author and reviewed by a second author.

Data were extracted according to pre-specified topics and subtopics complemented and adapted by topics and subtopics found in the documents. For the different types of documents from ISO, regulators and public-private research consortia, we provided general background information about their role in the regulatory system and how their recommendations were developed. The recommendations were summarized in a narrative synthesis and additionally presented in tables.

Results

A total of 30 regulatory guidance documents are reviewed in detail, including 19 from six national jurisdictions [Belgium 1, United Kingdom 3, Australia 2, Canada 1, Japan 1, United States of America 11]; eight from the EU; and three from the IMDRF (Table 28; and section 4.4Table 29Table 29). Twelve ISO standards are also reviewed (Table 3; and section 4.3), including three general standards relating to clinical investigations and risk management and nine specific standards relating to cardiovascular devices. No ISO standards covering clinical investigations for orthopedic high-risk

devices or high-risk devices for diabetes have been identified. Finally, four documents from regulatory-private research consortia were included (Table 6; and section 4.5).

Recommendations from regulatory guidance

The recommendations provided in the regulatory guidance documents fell into eight broad topics (Table 28, Table 40,Table 41,Table 42). These are discussed in detail throughout this report as follows:

Definition and classification of study types, levels of evidence *(section 4.4.1)*. Two documents, from the FDA in 2013 (Table 10) and from Australia in 2022 (Table 11), provide a classification and hierarchy of study designs that can be used, each of which is headed by a randomized controlled trial (see 4.4.1; and Table 29). The FDA guidance differentiates additionally the type of blinding and intends to advise study designs for market approval, whereas the TGA classification was developed in the context of clinical evaluation.

Need for a clinical investigation *(section 4.4.2,* Table 13*).* Six documents from four legislations and from the IMDRF recommend when a new clinical trial is required. All guidance documents demand a clinical evaluation of the existing evidence, to analyze if it is sufficient to confirm compliance with relevant essential requirements for safety and performance. New questions of safety, clinical performance and effectiveness and intended use are stated as general criteria for the need of a clinical trial. Some documents specify more concrete criteria. If equivalence to an approved device can be demonstrated, a clinical investigation is not necessary. Five documents contain recommendations for when devices can be considered equivalent. Criteria to consider are similar in most of the included documents, but what is accepted as predicate device differs.

Choice of study design for pivotal clinical investigations *(section 4.4.3,* Table 14*).* Six documents from four countries and the IMDRF make recommendations on the choice of study type. The IMDRF does not make a statement on any specific study design. In principle the regulatory authorities from the four jurisdictions judge the randomized controlled trial as the most valid study design for a pivotal confirmatory trial. They may also accept other designs, as long as concerns about validity can be addressed, but there seems to be a slightly different emphasis among regulators on the difficulty of achieving this goal. Some criteria are mentioned in all documents. A systematic and detailed discussion of advantages and disadvantages and when to use which type of control group is provided only by the FDA.

General design issues, investigation objective, and Population-Intervention-Population-Outcomes (PICO) *(section 4.4.4).* Two documents point out that the formulation of the study objective should provide the scientific rationale for the clinical investigation supporting the intended use in the target condition and supporting any claims that are made for labelling.

Eleven documents make recommendations about the study population. All of them state that the subjects in a trial should be representative of the target population, and three of the five authorities advise pre-specification of clearly defined eligibility criteria (Table 15). Much attention has been paid in North American countries to better representing and separately analyzing the results from groups of subjects who have previously been under-represented in trials. The FDA published four documents on that topic and Health Canada one on women in trials.

Six guidance documents contain recommendations on intervention or medical devices. Four provide detailed lists with items to describe.

Six documents give recommendations on comparators that are considered appropriate in a clinical investigation of medical devices. The most extensive guidance on study controls comes from the FDA.

Twelve documents from five legislations advise how to select endpoints and outcomes for device trials (see 4.4.4, and Table 18) with the FDA and MHRA providing more details. As shown in Table 18, four specify clinically meaningful endpoints that are important for the patient, and also validation of any surrogate endpoints.

Statistical methods *(section 4.4.5).* Fourteen guidance documents from six jurisdictions were included. Seven of them were issued from the FDA and five of them focused on specific methods such as Bayesian design or adaptive trials, and subgroup analysis in order to promote the collection, analysis and reporting of data on groups who have been under-represented in clinical trials so far. Pre-specification of all elements of the study design and analysis is demanded in most jurisdictions and the IMDRF.

Contextual factors and learning curve *(section 4.4.6).* Contextual factors and the learning curve are mentioned as a potential confounding factor by the TGA and in MEDDEV and IMDRF documents. The FDA guidance devotes more detailed attention to this issue, with respect to both data collection and analysis.

Reporting of clinical investigations *(section 4.4.7).* Sixteen documents from five jurisdictions (USA, Australia, EU, Belgium, UK) and the IMDRF recommend how to report clinical investigations in the regulatory setting. Relevant documents in all jurisdictions are the investigator's brochure (Table 23) considered in three documents, the clinical investigation plan, i.e. the study protocol (Table 24) considered in five guidance documents, and the clinical investigation report considered in four documents (Table 25).

All guidance on the investigator's brochure refer to Annex B of ISO 14155 as minimum requirement with some complements. Recommendations on the entire clinical investigation report are made only by the MDCG and TGA, which both refer to Annex D of ISO 14155. The TGA further refers to reporting guidelines for specific types of studies, from the EQUATOR network. The MDCG guidance adds some items to those listed in ISO 14155, such as a detailed description of the intervention. An important template for EU stakeholders to report clinical investigations of implantable and class III medical devices is the "Summary of Safety and Clinical Performance", which will be publicly available in EUDAMED. The items to be reported on clinical investigations that are listed in the MDCG guidance are shown in Table 26. A further template represents the minimum content of the clinical evaluation assessment report, which is used by notified bodies to document their conclusions of its assessment of clinical evidence (Table 27). Reporting of adverse events in a trial and the clinical investigation report is also subject of a MDCG guidance document.

Patient engagement in clinical investigations *(section 4.4.8).* In 2022 the FDA issued guidance on "Patient Engagement in the Design and Conduct of Medical Device Clinical Studies" that focuses on the application of patient engagement in the design and conduct of medical device clinical studies.

Areas suggested for patient engagement are the improvement of informed consent documents, input on barriers to recruitment unnecessary burden on study participants for data collection, discuss meaningful endpoints, informing the design of patient preference studies.

Methods used to derive recommendations

There are rarely exact descriptions in the guidance documents about how and with whose involvement the recommendations were developed. There is one indication in a MEDDEV document that stakeholders were involved. More details about their processes are presented in some FDA documents, generally due to the socially relevant background of disadvantage or to the desired participation of special groups. A report from 2011 describes the FDA guideline development process and gives recommendations for improvement.

The section on device-specific recommendations in the document issued by the TGA provides the methods for its rapid literature reviews that were used to derive endpoints or for other design characteristics. The guidance was published in 2022, the period of the literature search ended in 2015.

Recommendations from ISO standards and Regulatory-Private Academic Research Consortia

The general standard ISO 14155 on good clinical practice for clinical investigations of medical devices covers non-IVD devices of all risk classes (section 4.3) It does not establish a hierarchy of levels of evidence related to study designs for performing clinical investigations. The definition of design types used in ISO 14155, as “exploratory, confirmatory or observational”, is neutral with respect to level of evidence. A confirmatory study is an "adequately controlled" intervention study with pre-specified hypotheses for the primary endpoint(s) and the correct confirmatory statistical tests. Recommendations are very general and rarely study type specific. It includes annexes with reporting structures of the study protocol, the study report, and the "Investigator's Brochure". Regulatory guidance often refers to these annexes as minimum standards.

We included four ISO standards on implants for heart valves, and five on other cardiovascular implants. A detailed comparison of recommendations regarding the topics specified above is shown in Table 9.

All standards recommend a clinical investigation for all new devices or for expanded use of a device. Five standards (heart valves & standard on cardiovascular absorbable implants) recommend a randomized clinical trial for the clinical investigation of a new device, whereas the other four standards on cardiovascular implants recommend multi-center trials with a control group, or else a justification for no control group. ISO 5840-2 (heart valves) recommends incorporating objective performance criteria in the study design for established devices.

Regarding general design issues, the PICO specifications are especially relevant for device-specific recommendations. The degree of detail and elaboration of recommendations is different for the four elements and between standards. The standards for heart valves are all structured according to the same scheme, as are the standards for cardiovascular implants but using a different structure. The standards on heart valves give more detailed recommendations on study population, control group, statistical methods, whereas the other standards often use only general terms or refer to ISO 14155.

But all standards provide detailed recommendations for primary and secondary safety and effectiveness endpoints.

Two reports from the Medical Device Innovation Consortium (MDIC), and a report and a journal article from the Clinical Trials Transformation Initiative (CTTI) which resulted from the same project are included (section 4.5).

MDIC provides guidance on statistical methods to include external data in studies for regulatory decision making. References are made to studies that applied these methods and were then used successfully to support approval of medical devices or to modify their indications. In principle single arm studies are augmented by external data. Whether these methods are acceptable for approval depends on the relevance and reliability of the data.

The second publication defines twelve key components of a study protocol for randomized and observational medical device studies, that are applicable to different data sources. A template gives details of the content of these components. The intention was “to provide guidelines on what is required to conduct a scientifically valid medical device study”.

The CTTI developed recommendations how the suitability of registries for conducting registry-based randomized clinical trials can be assessed. The scope of the project was not restricted to medical device studies, but also comprised the conduct of trials for drugs, biologics, and procedures. Three central criteria are relevance, robustness and reliability of a registry.

Methods used to derive recommendations

There is no information in the general or device-specific ISO standards about the methods that have been used to develop recommendations. Thus, it is unclear how the current state of science in the field has been collected and taken into account. If the bibliography can be considered as an indicator which information was used, then taking into account of recommendations from the relevant academic research consortia of clinical experts seems to be an exception.

The methodology used to derive recommendations was described for MDIC and CTTI (see section 4.2.3.1).

Gaps

Objective Performance Criteria can be used as comparator for well-established devices. There seems to be no common terminology across regulators. Besides clarifying terminology, methodology is needed to derive and update performance criteria that considers confounding factors which may have a decisive impact on the safety and performance of a device. For device-specific guidance, it may be helpful to distinguish more clearly between mature and well-established technologies.

It may be useful to compare results from the CORE-MD systematic reviews on methodologies of clinical studies, with regulatory guidance for pivotal clinical investigations. A practice-oriented analysis may identify gaps where further regulatory guidance on study design would be helpful.

To identify research gaps in the study design of confirmatory studies relevant to practice, the experience of the notified bodies and expert panels providing an opinion on the evidence in the clinical evaluation assessment report could also be drawn upon.

From the perspective of the European regulatory system under the MDR, there is too little substantive guidance on evidence standards for the design of confirmatory studies for high-risk medical devices. Regarding trial methodology the MDCG published mainly guidance on reporting templates. Guidance on what quality of data is considered sufficient for approval is only available for the special case of additional evidence needed for legacy devices that have already been approved under the Medical Device Directives (MDCG 2020-6). However, this guidance is not about the study design of individual studies, but about the clinical evaluation of all available evidence on the medical device. Further there is no guidance on choice of study design from the MDCG. On the other hand, the FDA provides extensive guidance on this topic, including specific study designs such as adaptive and Bayesian designs, as well as topics that are also relevant in Europe, such as consideration of demographic subgroups, especially those under-represented in studies, and patient involvement in study design. For some of the recommendations regarding more complex study designs that require more individualized feedback between the manufacturer and the regulatory agency reviewing the marketing application, it is unclear how this could be implemented in the European system where the notified body responsible for certification is not allowed to provide guidance to the manufacturer.

Limitations

We may not have retrieved all relevant current documents from regulatory websites and ISO standards, although we have traced all the cross-references to other possibly relevant documents as well.

In order to provide a better overview of the similarities and differences between the recommendations, individual statements on each topic have been extracted and compared in tables. However, it is important to note that the scope (e.g. pivotal trials vs. trials at all stages) and purpose (e.g. submission forms, guidance on clinical evaluation, guidance on trial design) may differ. The legal background is also often not explicitly included, but other regulations may be included in separate documents or directly in legal acts without being mentioned. In addition, heterogeneous terminology is used.

Conclusions

There is detailed and systematic guidance on study design of high-risk medical devices from regulators available regarding level of evidence, need for a clinical investigation, choice of study design, general design issues and PICO, and statistical methods, but this guidance comes mainly from the FDA. Guidance from MDCG so far is predominantly limited to reporting templates, only the MEDDEV 2.7/1. revision 4 guidance document still issued under the Medical Device Directives contains more substance matter guidance on trials design, but from the viewpoint of clinical evaluation. For a better predictability what is considered appropriate study design under the MDR development of guidance for trial design by the MDCG is still needed.

For device-specific guidance on study design, whether from regulators or the International Organization for Standardization, a transparent, scientifically valid, and standardized methodology should be applied to collect and assess the current state of science on device-specific design issues.

To identify practically relevant research gaps in the study design of confirmatory studies, the experience of the notified bodies and expert panels providing an opinion on the evidence in the clinical evaluation assessment reports should be used.

1 Introduction

The Medical Device Regulation (MDR) of the European Union (EU) came into force in 2017 and has been applied since May 2021 (2017/745)[1]. The MDR has increased requirements for clinical investigations for market approval of new high-risk medical devices (e.g. A.11) but the regulation contains only general principles. The European Commission and the Medical Device Coordination Group have to implement the new regulation and therefore have to provide concrete guidance on the requirements for clinical investigations of high-risk medical devices (classes IIb and III).

In 2020 the European Commission awarded a Horizon 2020 grant to a consortium led by the European Society of Cardiology (ESC) and the European Federation of National Associations of Orthopedics and Traumatology (EFORT), that is reviewing methodologies of clinical investigations, advising on alternative designs, and developing recommendations for aggregating clinical data from registries and other real-world sources: the Coordinating Research and Evidence of Medical Devices (CORE-MD) project (965246 CORE-MD SC1-HCO-18-2020)[1].

This literature review has the task to identify, describe and compare existing guidance on clinical trial methodology for confirmatory pivotal trials of high-risk medical devices in the regulatory setting. In addition to guidance given by regulators, standards from the International Standardization Organization play a key role in the European regulatory system, as well as in other jurisdictions. Recommendations from public–academic research consortia may also be relevant if they address trial methodologies for medical devices in general.

For the evaluation of medicinal products, detailed guidance documents already exist from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)[2], and they are legally binding for market approval in the European Union. Many general principles of trial design also apply to medical devices, but some characteristics of medical devices necessitate specific guidance on trial designs for high-risk devices.

Medical devices are characterized by incremental development with short life cycles that may lead to device modifications during trials. Blinding of treatment arms may be prevented by the physical mechanism of action of a device. Equal recruitment and proficiency may be difficult due to provider and patient preferences. Implantable devices are often inserted into the body through highly invasive procedures which introduce the risk of complications from surgery in addition to any risks of device failure. Thus, linking outcomes to specific elements of the intervention may be challenging. Further contextual factors such as individual and institutional experience should also be considered when quantifying the effect of an intervention, to ensure an adequate implementation of findings ([2],[3],[4],[5],[6],[7]).

[1] https://eur-lex.europa.eu/eli/reg/2017/745/oj
[2] https://www.ich.org/

2 Objectives

This review has three aims:

1. to identify and describe guidance and recommendations on the methodology of design, conduct, analysis and reporting of confirmatory pivotal clinical trials of high-risk medical devices, from medical device regulators and international standardization organizations,
2. to compare similarities and differences of existing guidance, and
3. to identify gaps for further research on trial methodology with regard to implementation of regulatory guidance.

3 Methods

A study protocol was developed and then commented upon by the partners of Task 1.4 and Work Package (WP) 1 of CORE-MD, between June 2021 and November 2021. It was registered in the Open Science Framework on January 20th 2022[3].

Changes in the methods of this report, compared to the study protocol, are listed at the end of the methods (see 3.6).

3.1 Inclusion and Exclusion Criteria for Documents

We included guidance documents on the design, analysis and reporting of confirmatory pivotal clinical investigations to evaluate the clinical performance, effectiveness or safety of the investigational device. Study designs had to be interventional according to definition of ISO 14155: 2020 Annex I [8], but they may have been randomized or non-randomized. Clinical investigational designs for other phases of the life cycle of high-risk implantable medical devices were excluded; they will be analyzed in other WPs of CORE-MD (WP2, WP3).

We adopted the definition of clinical developmental stages and pivotal clinical investigations (see Table 1) from ISO 14155: 2020, Annex I [8]. We chose this definition because ISO 14155: 2020 is in the legislative process to become a harmonized European standard. After this process has been completed, a presumption of conformity will be conferred for any device which meets the requirements of this standard. Thus, definitions of ISO 14155 will be highly relevant for all aspects of trial design in the application for CE marking.

We focused on high-risk therapeutic medical devices such as implants (class IIb and III according to the MDR). General guidance documents for high-risk devices or broader definitions including high-risk devices were included. With regard to device-specific guidance, we included guidance relating to the indications selected for Task 1.1 of CORE-MD, i.e. cardiovascular and orthopedic high-risk devices, and high-risk devices for diabetes. We excluded guidance documents on software as a medical device, on machine learning, and on patient-reported outcomes, because they are the subjects of other tasks in CORE-MD.

[3] https://osf.io/3mf7v[4] ISO 16142-1: 2016. Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards.

Table 1. Clinical development stages according to ISO 14155:2020, Annex I (8)

Regulatory status	Pre – market		Post - market	
Clinical development stage	Pilot stage	Pivotal stage	Post – market stage	
Type of design	Exploratory or confirmatory	Confirmatory		Observational
Descriptors of clinical investigators	First in human clinical investigation Early feasibility clinical investigation Traditional feasibility clinical investigation	Pivotal clinical investigation	Post-market clinical investigation	Registry [1] Post-market clinical investigation
Burden to subject	Interventional			Non-Interventional

[1] Registry data may be used for pre-market regulatory purposes (see I.5.6), this can also apply to the post-market clinical investigation data.

We included guidance documents from these bodies:

- International Organization for Standardization (ISO),
- International Medical Device Regulators Forum (IMDRF),
- Medical Device Coordination Group of the European Union (MDCG),
- Regulatory authorities in EU countries, the United Kingdom, Norway, Switzerland, the United States of America, Canada, Australia and Japan.

We chose these countries because they are covering the same medical devices and technologies, and because they are high-income countries where regulators face similar tasks. In addition, we included published articles with recommendations from consortia in which regulators and academic medical experts are substantially involved, and articles from expert consensus groups on the topic. We excluded documents with device- or disease-specific guidance if they had been published before 2000 and more recent documents if they were judged to be out of date by the consortium experts.

3.2 Literature Search (Information Retrieval)

3.2.1 Websites

ISO standards and regulatory guidance documents are not included in bibliographic databases. Therefore, we searched the websites of ISO, international and national regulatory organizations, public-private research consortia, and umbrella organizations of notified bodies in Europe, between May 2021 and February 2022. We checked whether documents have been updated until December 2022. The websites, dates and search strategies are listed in the appendix.

3.2.2 Experts

We asked experts from the CORE-MD consortium to supplement our search results.

3.3 Literature Selection

3.3.1 International Organization for Standardization

We reviewed in detail the bibliography of ISO 14155:2020 “Clinical investigation of medical devices for human subjects — Good clinical practice”.

We used the list of 129 ISO standards given in ISO 16142-1: 2016[4] as the starting point to select others of possible relevance for high-risk implantable medical devices (in classes IIb and III); it lists all standards published until 2016. One reviewer screened the list and identified using the preview function on the ISO website those standards on high-risk medical devices that contained a chapter on clinical investigation. To check whether new relevant standards were published in 2016 and later, one reviewer searched the online browsing platform of ISO. A second reviewer from Team-NB who had access to all medical device-related ISO standards checked the full texts of the ISO standards identified by the first reviewer, to confirm whether they contained a chapter with substantial information on clinical investigation. A detailed description of the selection is shown in the Appendix. The search on the website was performed on May 18th, 2021.

3.3.2 Websites of regulators, public-private research consortia, and umbrella organizations of notified bodies

Documents from the internet search were screened and downloaded by one author and reviewed by a second author. We searched the websites in June 2021 and repeated the search in October 2021 and February 2022. A detailed description of the search and selection with reasons for exclusions is provided in the Appendix. The selection is shown in a PRISMA flow diagram [9].

[4] ISO 16142-1: 2016. Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards.

3.4 Extraction of Documents

For included documents containing guidance or recommendations, we described the recommendations according to the topics and subtopics shown in Table 2. Further topics and subtopics were specified as necessary, during data extraction; for example, the subtopic "Specific statistical and design approaches" was subdivided because additional topics were addressed in the included documents. We did not use the scheme for four documents from regulatory-private research consortia, which were summarized according to their structure.

We separated guidance on medical devices in general from guidance specific for high-risk devices in cardiovascular, orthopedic or diabetic indications.

Table 2. Main topics and subtopics used for data extraction.

Topics	Subtopics
Definition of study types, levels of evidence	
Need for a clinical investigation	Equivalence
Choice of study design for pivotal clinical trials	
General design issues	Study objective Study population Intervention Comparator Outcomes
Statistical methods	Statistical uncertainty Sample size calculation Pre-specification of statistical analysis Subgroup analysis Specific statistical and design approaches
Contextual factors and learning curve	
Reporting / documentation of clinical investigations	Study protocol Study report Investigator's Brochure
Patient engagement in clinical studies	

3.5 Data Analysis and Synthesis

For the different types of documents from ISO, regulators and public-private research consortia, we provided general background information about their role in the regulatory system and how their recommendations were developed.

The recommendations were summarized in a narrative synthesis. The synthesis presents the results separately for the documents of each stakeholder group. It is subdivided in the thematic sections shown in Table 2. Within sections, we separated guidance on medical devices in general from guidance specific for high-risk devices in cardiovascular, orthopedic, or diabetic indications. We summarized recommendations according to the topics for the included device-specific ISO standards. For clearer presentation of guidance from regulators we used tables to summarize recommendations on one topic from one guidance document, as well as to compare recommendations across regulators.

3.6 Data Analysis and Synthesis

3.6.1 Changes to the scope of this report

The objectives in task 1.4 of the CORE-MD project which were the basis of the study protocol comprised a larger group of institutions or stakeholders for the collection of recommendations than presented in this report. In addition to ISO, regulators, public-private research consortia, and medical professional societies, we had planned to include health technology agencies and academic research reports, but the high number and large volume of documents found did not allow to analyze all documents within the given time frame.

Therefore, this report analyses the recommendations from the central actors of the regulatory system, ISO standards, regulatory guidance and research consortia initiated by regulators and with their significant participation. Documents of HTA agencies, medical professional societies and academic research that were included in the literature search and selection, have been kept and will be analyzed in separate publications.

3.6.2 Changes to inclusion criteria

We limited the search to documents published since the year 2000. Although this choice is arbitrary, in many countries the legal and regulatory framework developed during the last 20 years, and technology also developed rapidly in the three selected medical fields. We excluded device-specific guidance if the consortium experts in the field considered them as outdated.

Due to the large number of identified documents, we only included recommendations from academic expert groups or research consortia that were based on consensus processes. We therefore included relevant publications from consortia including regulators such as the Clinical Trials Transformation Initiative (CTTI) or the Medical Device Innovation Consortium (MDIC) or the disease-specific Academic Research Consortia.

We excluded other recommendations from academic researchers on new trial designs such as registry-based trials. They will be considered in CORE-MD WP 2, Task 2.2 (on new trial designs).

3.6.3 Changes to data extraction and analysis

We did not directly extract recommendations from regulators in a table. Instead, we created a table indicating in which chapters or on which page numbers of the documents, the recommendations on

different topics are included. The reasons are that many regulatory documents are large and that long text passages in tables no longer provide clarity. In addition, regulatory documents are freely available, and it is easy to identify the relevant sections in the documents.

Further, we presented recommendations in a separate table for each of the other groups (ISO, disease-specific academic research consortia for regulatory setting, academic expert consensus on general issues for trial design) because this allows a clearer presentation.

We did not extract information on the strength of evidence of the recommendations, because such information was not provided for single recommendations. Instead, we extracted methods of how recommendations were derived for each document. If the methods were the same for documents of certain stakeholder groups, we described the methods for the whole group of documents.

4 Results

4.1 Results of Literature Search and Selection

4.1.1 International Organization for Standardization

A detailed description of the identification and selection is given in the appendix (A.2). After full text screening of the preliminary included documents, we excluded ISO 14283, ISO 14602, ISO 14630 because they did not contain recommendations on clinical investigations, other than references only to ISO 14155 and the Declaration of Helsinki. Finally, 12 standards were included (see Table 3). ISO 12417-1 was not yet the final version but a draft version which has already been published.

Table 3. Twelve included standards of the International Organization for Standardization (ISO) relevant to clinical investigations

Number / Publication year	Title of document (in English)
ISO 5840-1:2021	Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements
ISO 5840-2:2021	Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes
ISO 5840-3:2021	Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques
ISO 5910:2018	Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices.
ISO 7198: 2016	Cardiovascular implants — Tubular vascular prostheses - Tubular vascular grafts and vascular patches.
ISO 12417-1: 2021	Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products.
ISO 17137:2021	Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants. Part 1: General requirements.
ISO 25539-1:2017	Cardiovascular implants — Endovascular devices Part 1: Endovascular prostheses.
ISO 25539-2: 2020	Cardiovascular implants — Endovascular devices Part 2: Vascular stents.
ISO 14155 Third edition: 2020	Clinical investigation of medical devices for human subjects — Good clinical practice.
ISO 14971: 2019	Medical devices — Application of risk management to medical devices.
ISO 24971: (2020)	Medical devices — Guidance on the application of ISO 14971.

4.1.2 National regulatory authorities responsible for medical devices

Websites (URLs) and details of the selection of documents are given in the Appendix (A.3)

Until the end of our search in November 2021, we found no information on national medical device regulation at all, or any information on national or European legislation under the MDR, in the websites of regulators from 13 countries:

- Croatia
- Czech Republic
- Estonia
- Hungary
- Latvia
- Luxembourg
- Malta
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain

Seven regulators stated on their websites that the MDR is the relevant legislation for MD, or they presented national implementing acts, but they did not reference concrete guidance documents for good clinical practice (GCP) of clinical investigations other than the MDR:

- Bulgaria
- Cyprus
- Germany
- Greece
- Italy
- Lithuania
- Netherlands

Five regulatory authorities refer to ISO 14155:2020 and to the guidance of the Medical Device Coordination Group (MDCG):

- Austria
- Denmark
- Finland
- Ireland
- Sweden

The regulator in France refers only to MDCG for GCP. The regulator in Belgium refers to ISO 14155:2020 and summarizes its recommendations extensively: we included this document [10] (see Table 4) for analysis, but did not extract the synopsis of ISO recommendations.

Among **non-EU countries in Western Europe**, the regulatory authority in Norway published no documents with concrete recommendations for GCP, but its website refers to MDR and MDCG guidance. The Swiss regulator refers to MDR, ISO 14155 and MDCG guidance. Switzerland and the EU did not prolong their Mutual Recognition Agreement of certificates, but the legal adaptation to this situation had no impact on the recommendations on trial design. The regulator in the UK will not apply the European MDR (EU MDR), except for Northern Ireland. The UK legislation is based on an updated version of the EU MDD. Three guidance documents on the legislation ([11], [12], [13]) contain some guidance on trial design and were included for extraction and analysis of recommendations (see Table 4).

Among **regulatory authorities outside Europe** who have been considered relevant for this review, we identified 15 documents with recommendations on study design for clinical investigations or on questions related to this topic ([14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28]).

On the website of the **Food and Drug Administration in the USA**, we identified 11 documents with recommendations on trial design, the evaluation of benefit-risk balance of a medical device, or the determination of substantial equivalence (18-28). Six of these documents consider general design issues of premarket medical device trials, two deal with benefit-risk determination, one concerns the evaluation of substantial equivalence in premarket notifications, one contains recommendations for promoting the participation of women in studies, and another document considers patient participation in trial design. We excluded three documents that provided device-specific guidance within the field of cardiovascular devices ([29], [30], [31]), because they were too old to provide relevant guidance in this rapidly developing field. Device-specific guidance on other specialties (e.g. for prostate- or urinary tract-related health problems, and neurological diseases) were also excluded according to the inclusion criteria.

We identified one document from the regulatory authority **Health Canada Therapeutic Products Directorate** (TPD)([15]). It contains recommendations on the inclusion of women in trials with relevance to trial design. A document with recommendations on trial design for cardiovascular stents [32] was excluded because it was too old (2004) and therefore outdated. We included one guidance document on clinical evidence from the regulator in **Australia**, the Department of Health, Therapeutic Goods Administration (TGA)[14] and a second one from the National Health and Medical Research Council in Australia [17], because it was the basis for the "hierarchy of evidence" referred to in the TGA document. From the regulator in **Japan**, the Pharmaceuticals and Medical Device Agency of the Ministry of Health, Labor and Welfare (PMDA)[16], we included one document on clinical trial guidance.

Overall, 19 documents were included for extraction and analysis of recommendations on clinical trial design for pivotal premarket trials (see Table 4).

Table 4. Nineteen included documents from national regulatory authorities

Regulatory Authority	Title of document (in English)	Date of publication

FAMHP, Belgium	Clinical investigations – guidance on dossier content. Version 2	June 2021
MHRA, UK	Clinical investigations of medical devices – compiling a submission to MHRA	May 2021
MHRA, UK	Clinical investigations of medical devices – guidance for manufacturers	May 2021
MHRA, UK	Clinical investigations of medical devices – statistical considerations	May 2021
TPD, Canada	Considerations for inclusion of women in clinical trials and analysis of sex differences	2013
FDA, USA	Guidance for the use of Bayesian statistics in medical device clinical trials	2010
FDA, USA	Design considerations for pivotal clinical investigations for medical devices	2013
FDA, USA	Evaluation of sex-specific data in medical device clinical studies	2014
FDA, USA	The 510(k) program: Evaluating substantial equivalence in premarket notifications	2014
FDA, USA	Adaptive designs for medical device clinical studies	2016
FDA, USA	Collection of race and ethnicity data in clinical trials	2016
FDA, USA	Evaluation and reporting of age-, race-, and ethnicity-specific data in medical device clinical studies	2017
FDA, USA	Factors to consider when making benefit-risk determinations in medical device premarket approval and de novo classifications	2019
FDA, USA	Consideration of uncertainty in making benefit-risk determinations in medical device premarket approval, de novo classifications, and humanitarian device exemptions	2019
FDA, USA	Health of women. Strategic plan	2022
FDA, USA	Patient engagement in the design and conduct of medical device clinical studies	2022
TGA, Australia	Clinical evidence guidelines. Medical devices. Version 3	Nov 2021
NHMRC, Australia	NHMRC levels of evidence and grades for recommendations for developers of guideline	2009

PMDA, Japan	Release of clinical trial guidance to facilitate the speedy and accurate approval and development of medical devices	Mar 2017

FAMHP: Belgium Federal Agency for Medicines and Health Products, FDA: U.S. Food and Drug Administration, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), TGA: Department of Health, Therapeutic Goods Administration (Australia), TPD: Health Canada Medical Devices Bureau of the Therapeutic Products Directorate.

4.1.3 European Commission, the Medical Device Coordination Group and the International Medical Devices Regulation Forum

We checked all guidance documents on the website of the European Commission. For details of selection see Appendix A.3. We included one document related to the Medical Device Directives [33] and seven documents related to the MDR from the Medical Device Coordination Group ([34],[35],[36],[37],[38],[39],[40]).

On the website of the IMDRF we screened the titles of all available documents to gauge whether they may contribute recommendations to trial design of premarket pivotal trials. We included three documents ([41],[42],[43]) for extraction and analysis of recommendations. For details of selection see Appendix A.3. The included 11 documents are listed in Table 5.

Table 5. Eleven included documents from EC, MDCG and IMDRF

Regulatory Sources	Title of document (in English)	Date of publication
MDCG	MDCG 2019-9 Summary of safety and clinical performance. A guide for manufacturers and notified bodies	Aug 2019
	MDCG 2020-05: Clinical evaluation – equivalence. A guide for manufacturers and notified bodies	Apr 2020
	MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies	Apr 2020
	MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 and MDCG 2020-10/2 clinical investigation summary safety report form v1.0	May 2020
	MDCG 2020-13 Clinical evaluation assessment report template	July 2020
	MDCG 2021-06 Q& A regarding clinical investigations	Apr 2021
	MDCG 2021-08 Clinical investigation application/notification documents	May 2021

EC	MEDDEV 2.7/1 revision 4: Clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC	Jun 2016
IMDRF	Clinical Investigation	Oct 2019
	Clinical evaluation	Oct 2019
	IMDRF terminologies for categorized adverse event reporting (AER): terms, terminology structure and codes	Mar 2020

EC: European Commission, IMDRF: International Medical Device Regulators Forum, MDCG: Medical Device Coordination Group.

4.1.4 Regulatory – private research consortia dealing with medical devices

We searched the websites of the Medical Device Innovation Consortium (MDIC), the Clinical Trials Transformation Initiative (CTTI), and the National Institute for Health in the USA. For details of the selection see A.4. We included four publications, dealing with a methodological framework for the use of real-world evidence throughout the medical device total product life cycle [44], statistical methods [45], how to determine the suitability of registries to embed clinical trials [46], and registry trials in general [47] (Table 6).

Table 6. Four included documents from the Medical Device Innovation Consortium and the Clinical Trials Transformation Initiative

Institution	Title of document (in English)	Date of publication
MDIC	National Evaluation System for health Technology Coordinating Center (NESTcc) Methods Framework. A Report of the Methods Subcommittee of the NEST Coordinating Center – An initiative of MDIC	2020
	External Evidence Methods (EEM) Framework. Statistical Methods for Leveraging External Data in Regulatory Decision-Making. A Report of the EEM Working Group of the Medical Device Innovation Consortium (MDIC). Draft.	2021
CTTI	Mikita JS, Mitchel J, Gatto NM, Laschinger J, Tcheng JE, Zeitler EP, et al. Determining the suitability of registries for embedding clinical trials in the United States: A project of the Clinical Trials Transformation Initiative. Ther Innov Regul Sci. 2021; 55: 6-18.	2021
	CTTI Recommendations: Registry Trials	2017

CTTI: Clinical Trials Transformation Initiative, MDIC: Medical Device Innovation Consortium.

4.2 Types of Documents Included

4.2.1 ISO standards

Harmonized European standards are a key element of the EU governance of medical devices. The legislation covers essential requirements that must be met by products intended to be placed on the EU market, but for details it refers to "the technical details and solutions supporting those essential requirements laid down in harmonized European standards specifically developed by designated European standardization organizations on the basis of specific standardization requests issued by the Commission" [48].

Harmonized European standards are published in the Official Journal of the European Union (OJEU). As already mentioned in relation to ISO 14155, their use confers presumption of conformity of the product with the legal requirements that the related standard aims to cover. But the use of harmonized standards is voluntary, at the discretion of the manufacturer.

Harmonized European standards in the field of medical devices are developed by two European standardization organizations (ESOs), which are the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC). Standardization requests under the MDR/IVDR are intended to be regularly revised and updated, to ensure continuous adaptation to the European and international standardization work and innovation of medical devices. European standards are developed in parallel to international standards produced by the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). The three agreements that have set out cooperation between the international and European bodies (Vienna Agreement 1991, Dresden Agreement 1996, Frankfurt Agreement 2016) state that the normative texts of the standards are substantially the same. European standards contain in addition a European foreword and an annex Z which links the clauses of the standards to the relevant requirements of the MDR.

According to the homepage of the European Commission on harmonized European standards[5] and the "Summary of references of harmonized standards published in the OJEU" generated on 17 May 2022, the following ISO standards included in the CORE-MD review are harmonized European standards to the MDR:

- ISO 14971: 2019

And these older versions are still harmonized European standards to the MDD:

- EN ISO 5840: 2009
- EN ISO 25539-1: 2009
- EN ISO 25539-2: 2009
- EN ISO 14155: 2011

[5] https://www.medical-device-regulation.eu/mdr-resource-harmonized-standards-lis/

According to the database[6] and the M/575 Commission Implementation Decision of 4 April 2021, standardization has been requested for ISO 14155: 2020, ISO 5840-1, -2 and -3: 2021; for ISO 12417: 2021; and for ISO 25539-1: 2017 and -2: 2020.

TS 17137:2021 is a technical specification and not eligible for harmonization.

For the remaining included standards (ISO 5910: 2018, 7198: 2016) we retrieved neither a harmonized European standard, nor a standardization request.

4.2.1.1 Methods of development of recommendations

Although extensive guidance exists on the processes and methods to be followed when developing ISO standards[7], none of the ISO standards included in this review reports how their recommendations were developed, such as whether a systematic literature search on the topic was done and if yes, how it was done.

4.2.2 Guidance documents of national regulators, the European Union, and IMDRF

Guidance documents of national regulators, the European MDCG and the IMDRF are not legally binding. This is usually stated in each guidance document. In MDCG documents it is also stated that a binding "shall" is used when there is a corresponding "shall" in the MDR, otherwise "should" or "recommended" etc. is used indicating the interpretation of the MDR." We also included a guidance document issued under the Medical Device Directives, MEDDEV 2.7/1 Rev. 4 [33], since it is considered still to apply to many provisions in the MDR which are listed in Appendix I of MDCG guidance document 2020-6 [38].[8]

On the website for FDA guidance documents for medical devices[9] it is stated that "Guidance documents do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statue, regulations, or both." A similar text is found in every FDA guidance document, before the introduction.

The IMDRF is a voluntary group of medical device regulators world-wide that builds on the work of its predecessor organization the Global Harmonization Task Force on Medical Devices. It "aims to accelerate international medical device regulatory harmonization and convergence"[10] but its recommendations also have no legal binding force. Current members are Australia, Brazil, Canada, China, the European Union, Japan, Russia, Singapore, South Korea, the United Kingdom and the United States of America.

[6] https://ec.europa.eu/growth/tools-databases/mandates/index.cfm?fuseaction=search.welcome
[7] https://www.iso.org/directives-and-policies.html; https://www.iso.org/iso-guides.html
[8] Revision of MEDDEV 2.7/1 to update it to comply with the MDR, started during 2023.
[9] https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products
[10] https://www.imdrf.org/about

4.2.2.1 Methods of development of recommendations

There is rarely a hint on how recommendations are developed, but some authorities have a process for public consultation. The **FDA** provides the possibility to comment within 60 days after the draft is published, on most level 1 guidance documents, which are those that:

(1) set forth initial interpretations of statutory or regulatory requirements,

(2) set forth changes in interpretation or policy that are of more than a minor nature,

(3) include complex scientific issues, or

(4) cover highly controversial issues.

Level 2 guidance sets forth existing practices or minor changes in interpretation or policy [49]. Another report published in 2011 [50] described the guidance development process at the FDA, but we did not find any further document about whether or not its recommendations were implemented. In five of the included FDA documents ([21], [23], [24], [27], [28]) some information is mentioned about the preparation of the guidance (see Table 7).

Table 7. Information on guidance development in FDA documents

Guidance Document	Method of recommendation development
FDA 2022 Patient Engagement [28]	The guidance document was based on the discussion in two meetings of the FDA's Patient Engagement Advisory Committee (PEAC) in October 2017 and November 2018, further the results of a public workshop convened by the FDA and the Clinical Trials Transformation Initiative (CTTI) on March 18, 2019. "Before issuing this guidance document, FDA released a discussion document to facilitate further public discourse on patient engagement in medical device clinical trials. The discussion document described FDA's initial thoughts about patient engagement and its potential impact on medical device clinical studies. The discussion document included targeted questions on which the Agency sought public feedback through an open public docket." Public feedback was also sought during the second PEAC meeting. Comments from the meetings and from the public docket were considered in completing the guidance.
FDA 2022 Health of Women [27]	In the guidance document the development of the "Health of Women" regulatory landscape is described. Documents mentioned on which the strategy paper is based are an FDA report on demographic subgroup analyses and public disclosure of information from sources including Premarket Approval Applications for class III devices, published in 2013, and the guidance document titled Evaluation of Sex-Specific Data in Medical Device Clinical Studies, and a policy document on sex as a biological variable from the National Institute for Health.
FDA 2017	"Prior to developing the policy set forth in this guidance, FDA publicly sought input from a variety of experts and stakeholders regarding the study and

Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies [24]	evaluation of age, race, and ethnicity in clinical studies for medical devices. On April 9, 2015, the Institute of Medicine convened a public workshop of various government agencies, physician professional societies, and patient advocacy groups to discuss strategies for ensuring diversity, inclusion, and meaningful participation in clinical trials. This guidance document reflects the recommendations generated in this and other public fora." (Section III)
FDA 2016 Collection of Race and Ethnicity [23]	"Prior to developing the recommendations set forth in this guidance, FDA publicly sought input from a variety of experts and stakeholders regarding the study and evaluation of age, race, and ethnicity in clinical studies for medical products. On April 1, 2014, FDA convened a public hearing for feedback on the findings of the FDASIA 907 Report, to obtain input on the issues and challenges associated with the collection, analysis, and availability of demographic subgroup data (i.e. age, sex, race, and ethnicity) in applications for approval of FDA-regulated medical products. FDA also opened a public docket for further input. On April 9, 2015 and December 2, 2015, various government agencies, physician professional societies, and patient advocacy groups participated in public workshops to discuss strategies for ensuring diversity, inclusion, and meaningful participation in clinical trials." (Section III)
FDA 2014 Sex-Specific Data in Medical Device Clinical Studies	"Prior to developing the policy set forth in this guidance, FDA publicly sought input from a variety of experts and stakeholders regarding the study and evaluation of women in clinical studies for medical devices. On June 2, 2008, various government agencies, physician professional societies, and patient advocacy groups participated in a public workshop to discuss ways to overcome barriers to understanding the impact of sex differences on clinical outcomes, with a focus on clinical study conduct and statistical analysis. On December 9, 2008, FDA's Center for Devices and Radiological Health (CDRH) and an industry trade association co-hosted a second public meeting to facilitate discussion in anticipation of issuance of FDA guidance on this subject." (Section III)

FDA: U. S. Food and Drug Administration.

For **MEDDEV guidance** it is stated that "The Guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector" [33]. There is no information on how MDCG guidance is developed, however, and no possibility for general public comments. The MDCG currently has 14 Working Groups, whose terms of reference are published in detail[11] but without

[11] https://health.ec.europa.eu/medical-devices-dialogue-between-interested-parties/medical-device-coordination-group-working-groups_en#three

information on how recommendations are developed. We did not find any information on the websites of Health Canada, TGA or PMDA about how their guidance documents are developed.

The **TGA guidance** document included in this report [14] had a methods section describing how the "source material" was retrieved used for the development of the device-specific recommendations. The literature search and the classification of study types were shortly described in the appendix. For the literature search the a priori defined inclusion criteria, search strategies for each device class and databases in which the searches were conducted, as well as time restrictions were provided.

The **IMDRF** working groups develop guidance called "technical documents". The "Terms of Reference" document [51] states that "WGs [working groups] responsible for developing technical documents would generally involve the participation of stakeholders that have significant involvement in the development, manufacture or use of medical devices including, but not limited to, regulated industry, international entities and associations, academia, patient and consumer groups, medical professionals, and other regulatory authorities." But there are also closed working groups in which mainly regulatory authorities can participate. For example, the Working Group on Clinical Evaluation, which issued two [41], [42] of the included guidance documents, is a closed working group. The Working Group on Adverse Event Terminology is not categorized as a closed working group but consists only of regulators. There is a process of public consultation for draft guidance documents, but there is no description of that process. IMDRF guidance documents include a bibliography listing sources that were used, but not a description of their methodology.

4.2.3 Consensus documents of regulatory-private or academic research consortia

The Medical Device Innovation Consortium (MDIC) in the USA was founded in 2012 as a private-public partnership between the FDA and industry. Membership and participation is further open for nonprofit and government organizations "that are substantially involved in medical device research, development, treatment, or education; or in the promotion of public health; or that have expertise or interest in regulatory science" [45]. According to the charter of MDIC [52] its goals include to "[a]dvance the field of medical device regulatory science and its acceptance and use by the device industry" and to "[v]alidate and qualify new methods, tools, approaches, and standards that CDRH [Center for Devices and Radiological Health] may adopt as part of the regulatory process." The MDIC currently has 11 working groups, some of have developed guidance documents that were also subject to public commenting. MDIC documents contain a disclaimer that their general recommendations do not imply FDA concurrence for specific applications, do not represent the opinion or policy of the FDA or the companies represented, and do not necessarily reflect the official policy or position of MDIC, but are the views and opinions of the authors.

The Clinical Trials Transformation Initiative (CTTI) is a public–private partnership founded in 2007 by the Duke Clinical Research Institute and the US FDA. Its mission is "to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. The scope of the project is not limited to medical device trials. CTTI projects utilize multi-stakeholder project teams that follow an

evidence-based methodology to identify impediments to research, gather evidence to identify gaps and barriers, explore results by analyzing and interpreting findings, and finalize solutions by developing recommendations and tools" [46]. A paper describes how the CTTI selects topics, gathers evidence, analyses and interprets findings, and how it develops, disseminates and implements recommendations [53].

4.2.3.1 Methods of development of recommendations

The **MDIC** documents do not contain a detailed methods section describing how their recommendations were derived. The subcommittee developing guidance for a study protocol for medical device studies [44] held monthly meetings, and then a draft version was circulated to Network Collaborators for review and comment, followed by a period for public comment. Comments were incorporated and a 'Public Comment Response' was published on their homepage. The second guidance document [45] in an appendix includes the survey that was sent to industry statisticians on the use of external data in clinical studies, which was one of their sources. There is a further note to related work in which other MDIC documents are cited, and to its National Evaluation System for health Technology Coordinating Center (NESTcc), which provides frameworks that are characterized as living documents in that they will be moving toward a more complete version in future iterations.

A publication [46] on the **CTTI** guidance document on the suitability of registries for registry trials in addition, includes a methods section containing with some general information on the retrieval of evidence, the interviews with subject matter experts, and the expert meetings.

4.3 Recommendations for Clinical Investigations for Medical Devices from ISO Standards

We included three ISO standards which relate to medical devices in general ([54],[55],[56]):

ISO 14155: 2020 covers the good clinical practice of clinical investigations of medical devices for human subjects except in vitro diagnostic devices,

ISO 14971: 2019 and 24971: 2020 cover the application of risk management to medical devices.

The other nine standards ([57],[58],[59],[60],[61],[62],[63],[64],[65]) relate to cardiovascular implants.

4.3.1 Scope, structure, and parts relevant for trial design in ISO 14155, 14971 and 24971

ISO 14155: 2020 "addresses **good clinical practice** for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices" [54]. General requirements are specified that intend to protect human subjects, guarantee the scientific conduct of the clinical investigation and the credibility of its results, define the responsibilities of sponsors and principal investigators and assist the stakeholders involved in the conformity assessment of medical devices [54]. We considered mainly the parts directly relevant for study design and reporting:

- Chapter 1: Scope,
- Chapter 2: Normative references,
- Chapter 3: Terms and definitions,
- Chapter 4: Summary of good clinical practice principles,
- Chapter 6: Clinical investigation planning,
- Annex A: clinical investigation plan (CIP),
- Annex B: Investigator's brochure (IB),
- Annex D: Clinical investigation report (CIR),
- Annex F: Adverse event categorization,
- Annex H: Application of ISO 14971 to clinical investigations, and
- Annex I: Clinical development stages.

We partly considered chapters 7- 10 dealing with the conduct and termination of the clinical investigation, and the responsibilities of the sponsor and principal investigator. We did not consider chapter 5 on ethical considerations.

ISO 14971: 2019 "specifies terminology, principles, and a process for **risk management** of medical devices, including software as a medical device and in vitro diagnostic medical devices. The process described in this document intends to assist manufacturers of medical devices to identify the hazards associated with the medical device, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls" [55]. The scope of risk management is the whole life cycle of medical devices, but it is not intended to apply to "decisions on the use of a medical device in the context of any particular clinical procedure". Objective criteria for risk acceptability have to be established by the manufacturer.

ISO 24971: 2020 "provides guidance on the development, implementation and maintenance of a risk management system for medical devices according to ISO 14971: 2019" [56]. ISO 14155 (see Annex H) has already applied ISO 14971: 2019 to clinical investigations of medical devices. We therefore only supplemented central concepts of the risk management standards that are not operationalized or explained in ISO 14155 such as criteria for risk acceptability, risk analysis, benefit-risk analysis, and evaluation of overall residual risk.

4.3.2 Scope, structure and parts relevant to trial design of device-specific standards

Nine selected standards concern cardiovascular implants ([57], [58],[59],[60],[61],[62],[63],[64],[65]):

- ISO 5840 parts 1, 2, and 3: 2021 all relate to cardiac valve protheses,
- ISO 5910: 2018 relates to cardiac valve repair devices,
- ISO 7198: 2016 addresses tubular vascular grafts and vascular patches,
- ISO 17137: 2021 cardiovascular absorbable implants,
- ISO 25539-1: 2017 endovascular prostheses,
- ISO 25539-2: 2020 vascular stents, and

- ISO/DIS 12417-1: 2021 is a draft international standard on general requirements for vascular device-drug combination products.

All these standards contain a detailed chapter on clinical evaluation or on clinical investigations (CI) and most also include relevant annexes. All standards refer to ISO 14155 which should be applied for CI. Seven standards ([57], [59], [61], [62], [63], [64], [65]) listed ISO 14155 in the section on "Normative references" that must be applied.

The recommendations of the 12 included ISO standards are structured along seven topics:

- definition of study types,
- need for a clinical investigation,
- choice of study design for pivotal clinical investigations,
- general design issues, investigation objective, and PICO,
- statistical methods,
- contextual factors and learning curve, and
- reporting of clinical investigations.

Within the topic sections below, we first describe recommendations in standards that apply to all medical devices, from ISO 14155 and when relevant ISO 14971 and ISO 24971, and then recommendations from the nine specific ISO standards.

4.3.3 Definition of study types

ISO 14155 provides a classification of possible types of clinical investigations at different clinical development stages of a medical device, in Annex I (see Table 1).

The **pivotal clinical investigation**, on which this CORE-MD report focusses, is defined as:

> "A confirmatory clinical investigation designed to collect data on the clinical performance, effectiveness or safety of a device for a specified intended use, typically in a statistically justified number of human subjects. It can or cannot be preceded by an early and/or a traditional feasibility clinical investigation."

Further a **confirmatory clinical investigation** is defined as:

> "an adequately controlled clinical investigation in which the hypotheses of the primary endpoint(s) are stated before the start of the clinical investigation in the CIP and are analyzed in accordance with the CIP (i.e. sound confirmative statistical testing is pre-specified, intended, and applied)."

The CIP, an acronym for 'clinical investigation plan' is the study protocol of the CI. Other study types that precede the pivotal clinical investigation during the clinical development stages of a device are:

- first in human clinical investigations,
- early feasibility clinical investigation, and
- traditional feasibility clinical investigation.

The last stands in direct relation to the pivotal CI: it "is commonly used to capture preliminary clinical performance, effectiveness or safety information of a near-final or final device design to adequately plan an appropriate pivotal clinical investigation." A study type after the pivotal CI belonging to the post-market stage is the registry.

In annex A, which describes mandatory content of the CIP, "the design type of clinical investigation to be performed" is required, and as descriptive examples these terms are mentioned: "randomized, blinded or open-label, parallel groups or crossover, multicenter, international" (A.6). The objectives of the study should be "described as 'superiority', 'non-inferiority' or 'equivalence', if applicable."

Seven of the nine device-specific standards refer to ISO 14155 as a normative reference ([57], [59], [61], [62], [63], [64], [65]), but depending on the year of publication this may refer to different versions of ISO 14155. Only ISO 7198 explicitly states that the version from 2011 is meant. ISO 25539-1 and 25539-2 do not have ISO 14155 in the list of normative references, but state in clause 8.7 on clinical evaluation that CI should be performed "[…] using the principles of ISO 14155 or an equivalent publication". Of the nine standards for heart valves and cardiovascular implants, two standards (ISO 7198 Vascular grafts and patches, ISO 25539-1 Endovascular prostheses) provide a classification of study designs with six study types that should be used:

1. randomized, multi-arm, "unblinded" study with a concurrent control using an alternative or no treatment;
2. non-randomized study with concurrent control;
3. single-arm study with patient serving as own control (include designed single-arm crossover);
4. single-arm study with historical control using patient-level data;
5. single-arm study with literature control;
6. single-arm study with performance goals." (ISO 7198 10.1.3; ISO 25539-1 8.7.2)

This is the same as the classification used by the FDA (see section 4.4.1). In ISO 25539-2 (Vascular stents) which was published three years later, the six study types are not listed any more but these examples for "appropriate terms" to describe study designs description are provided: "number of study arms, type of control (randomized, literature, performance goal), blinding, prospective vs retrospective". The remaining seven standards for cardiovascular implants ([57], [59], [61], [62], [63], [64], [65]) do not provide a classification of study types or guidance on terminology for study designs.

4.3.4 Need for a clinical investigation

In ISO 14155, the decision to perform a trial is addressed under risk management (6.2.1):

> "The decision to embark upon or continue a clinical investigation of an investigational medical device requires that the residual risk(s), as identified in the risk analysis, as well as risk(s) to the subject associated with the clinical procedure including follow-up procedures required by the CIP be balanced against the anticipated benefits to the subjects."

For risk analysis of the medical device and its related procedure, ISO 14155 refers to ISO 14971: 2019 “Medical devices – Application of risk management to medical devices” [55]. Risk analysis consists of four elements:

- documentation of intended use and reasonably foreseeable misuse of the particular device being considered,
- identification of characteristics related to safety,
- identification of hazards and hazardous situations, and
- risk estimation. (4.1, 5.2-5.5)

“For each identified hazardous situation, the manufacturer shall estimate the associated risk(s) using available information or data. For hazardous situations for which the probability of the occurrence of harm cannot be estimated, the possible consequences shall be listed for use in risk evaluation and risk control” (5.5).

ISO 14971 is accompanied by ISO 24971 [56], which is a guidance on the application of ISO 14971. This standard contains an annex A comprising eight pages with questions for the identification of hazards and characteristics related to safety of medical devices. The informative annex C on the relation between the policy, criteria for risk acceptability, risk control and risk evaluation explain how the criteria for risk acceptability can be used in risk control and risk evaluation. ISO 14155 further demands that the “risk assessment shall include or refer to an objective review of published and available unpublished medical and scientific data” (6.2.2).

Eight of the nine device-specific standards state that a clinical investigation shall be performed for new devices and expanded indications of use or new applications of existing devices ([57], [58],[59],[60],[61],[62],[63],[64]). In draft standard ISO 12417-1, a clinical investigation shall be performed for devices “incorporating design characteristics for which the safety and effectiveness have not been previously demonstrated” (7.3.1).

A scientific justification is required for modifications of devices, if no clinical investigation is performed, in seven of the standards (57-63). Three of these specify the modifications of devices for which a CI should be performed as “significant design changes that can impact safety and performance” ([57], [58], [60]). ISO 5840-3 in addition mentions “minor modifications to clinically well documented devices”, for which omission or abbreviation of CI should be justified. Mainly the seven standards refer explicitly to risk assessment as the basis for justification. ISO 25539-2 points out that the “justification should include comment on the relevance of any differences between the subject device and the device used in the previous study and the relevance of any differences in the intended uses” [60]. The ISO 5840 standards ([61], [62], [63]) and ISO 5910 [59] explicitly mention that for “design changes of marketed devices that might affect safety and effectiveness” the need for a CI shall be determined by a risk analysis.

ISO/DIS 12417-1 uses a different formulation for the requirement of a CI: “Included in the clinical investigation shall be appropriate testing of any VDDCP [vascular device-drug combination product] incorporating design characteristics for which the safety and effectiveness have not been previously

demonstrated". It is not specified whether new devices or which modifications may meet this definition. The introduction states that:

"Many vascular device-drug combination products have been shown to be safe and effective in clinical use. This revision is not intended to require additional evaluation of these products as the testing would not provide useful information regarding the expected clinical performance of the product. Manufacturers can rely on historical data gathered under the specifications of the previous edition. Similarly, for product modifications or changes in intended clinical use, this revision is not intended to require additional evaluation of any aspects of the product that are not expected to change clinical performance."

4.3.5 Choice of study design for pivotal clinical investigations

ISO 14155 gives general recommendations for the choice of study design, not only related to pivotal clinical investigations:

> "The results of the clinical evaluation and the risk assessment shall be used to determine the required clinical development stages (see Annex I) and justify the optimal design of the clinical investigation. The clinical evaluation shall also help to identify relevant endpoints and confounding factors to be taken into consideration and serve to justify the choice of control group(s) and if applicable, comparator(s), the use of randomization or blinding, and other methods to minimize bias." (6.3)

ISO 14155 also characterizes the clinical evaluation:

> "The clinical evaluation includes an assessment and analysis of clinical data concerning clinical performance, effectiveness or safety of the investigational device or similar devices or therapies. The evaluation shall be relevant to the intended purpose and the proposed method of use of the investigational device or similar devices or therapies. This is a scientific activity that shall be done with rigour and objectivity according to scientific standards […]." (6.3)

Annex A.3 outlines the information that should be included in the CIP, and lists three items that the justification of the study design should comprise:

> a) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable carried out to justify the use of the investigational device in human subjects,
>
> b) an evaluation of clinical data that are relevant to the proposed clinical investigation,
>
> c) a description of the clinical development stage (see Annex I), if appropriate."
>
> The objective(s) of the investigation determine(s) whether an exploratory or a confirmatory design is appropriate to ascertain that the objectives of the clinical investigation can be reached." (6.4)

As further factors to take into account for a decision on study design are mentioned:

"clinical investigation objectives, subject selection, subject endpoint(s), stratification, investigation site selection, and comparative clinical investigation designs." (6.3)

From the above definition of a confirmatory clinical investigation (Definition of study types), it can be deduced that the study has to be at least "adequately controlled", with pre-specified hypotheses of the primary endpoint(s) and with sound confirmative statistical testing (Annex I 4.3). In Annex A.5 it is stated that the absence of controls shall be justified.

Five of nine standards on heart valves or cardiovascular implants (59, 61-64) recommend a randomized controlled trial (RCT) for pivotal clinical investigations. As reason for this choice, the ISO 5840 series (7.4.2; 7.4.1) and ISO 5910 (7.4.1) gives ethical considerations and the minimization of bias, and they state that an RCT may promote the adoption of effective therapies. ISO 17137 directly states: "A randomized trial powered for detection of differences with an existing control device is recommended" (5.7.3). However, in the ISO 5840 series and ISO 5910 there are also qualifications such as "Study designs may vary depending on the purposes of the assessment and/or the technology (novel technology versus modification to well-established device" (ISO 5840-2 7.4.2). "Novel devices include devices with characteristics […] that have never been evaluated clinically. 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 may be appropriate" (ISO 5840-2 7.4.6.3). "The use of objective performance criteria (OPC) is the recommended method for the statistical evaluation of adverse event data for new devices based on established device designs" (ISO 5840-2 7.4.6.2). The remaining four standards ([57], [58], [60], [65]) demand a multicenter study with at least three sites and a control group. If a control group is not included, this has to be justified and the method for outcome evaluation has to be prospectively specified (see ISO 7198 10.1.3; ISO 12147 7.3.3; ISO 25539-1 8.7.3; and ISO 25539-2 8.7.3).

4.3.6 General design issues, investigation objective, and PICO

In ISO 14155, the objective of a CI is defined as the main purpose for conducting the CI (3.37). In 6.3 it is stated that the "clinical investigation should be designed to allow confirmation of the benefit-risk analysis of the investigational device as outlined in the risk management report". In Annex A.5 it is further explained that the objective "shall relate to the hypotheses and corresponding endpoints relevant to the target population. The objectives of the clinical investigation shall translate directly into the pre-specification and operationalization of the primary endpoint(s). Claims shall be linked to eligibility criteria for subject and users." The CIP should contain primary and secondary objectives described as superiority, non-inferiority, or equivalence, scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, primary and secondary hypotheses and risks and anticipated adverse device effects that are to be assessed (A.5). Annex A.4 discusses how the elements of risk analysis and management regarding CI have to be described: anticipated clinical benefits, anticipated adverse device effects, risks associated with participation in the CI, possible interactions with concomitant medical treatments as considered under the risk analysis, steps to control or mitigate the risks, and rationale for benefit-risk ratio. Further in the normative Annex B on the mandatory content of the investigator's brochure, the risk management of the investigational

device has to be described, consisting of a summary of the benefit-risk analysis including identification of residual risks and contra-indications and warnings for the investigational device (B.4).

A.6 lists the items that have to be described regarding the design of the CI:

- the study type of the CI to be performed (see Definition of study types),
- description of the measures to avoid bias (randomization, allocation concealment, blinding, management of potential confounders), and
- the completion of the CI (last visit of the last subject, complete follow-up) (A 6.1).

Any known or foreseeable factors that can compromise the outcome of the CI or the interpretation of the results (A 6.4 c), should also be listed, together with the methods for addressing them (A 6.4 d). Examples that are given include subjective baseline characteristics, concomitant medication, use of other medical devices, and subject-related factors such as gender, age, or lifestyle. Methods to address them are subject selection, study design such as stratified randomization, or statistical analysis.

Four of the five standards on cardiovascular implants ([57], [58], [60], [64]) define the purpose of the CI as to assess the safety and effectiveness of the device under consideration. Three of them ([57], [58], [60]) add that the investigation is not intended to demonstrate the long-term performance of the device. ISO 12417 states that the purpose of the CI is to "provide reasonable assurance of safety and to evaluate the performance" of the device. All five standards require investigators to operationalize safety and effectiveness by more "specific aims" of the CI, and they suggest what can be included in these aims.

In the four standards on heart valves ([59], [61], [62], [63]) it is stated that the "clinical investigation program shall be designed to provide substantial evidence of acceptable safety and effectiveness to support the intended labelling for the device". Before a pivotal trial is started, pilot phase studies should be considered to provide initial information on safety and effectiveness (ISO 5840-3, 5910) or to optimize the device and patient selection (ISO 5840-2). "A scientific justification is required if pilot phase studies are not undertaken"([59], [61], [62], [63]).

Study population: In ISO 14155 there is no explicit recommendation on the characteristics of the study population of a CI, but it "shall be designed to evaluate whether the investigational device is suitable for […] the population for which it is intended" (6.3). The relationship between the investigated population and the target population, and eligibility criteria, have to be described in the CIP (A.6.3). In section 6.8 it is also recommended that "[t]he investigation site's facilities should be similar to the facilities required for the intended use of the investigational device(s) […]".

The four standards on heart valves ([59], [61], [62], [63]) state that the "study populations shall be representative of the intended post-market patient population, including etiology and pathology". Further, for pivotal clinical investigations it is stated that:

> "CI shall be designed to include enough subjects, investigators, and institutions to be representative of the intended patient and user populations to provide generalizable results. The design should 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 intended patient population shall be specified and any salient differences between the intended population and those studied shall be justified. The study should only include patients who are willing and able to participate in the follow-up requirements."

In addition, 14 disease- and device-specific "inclusion criteria to consider, ensuring that the expected benefit of the treatment outweighs the risk to subjects" are listed (7.4.5) (see Supplementary Table). Requirements mentioned for institutions in which pivotal CI are conducted, are: "institutions with appropriate facilities, case-load, and case-mix" and "investigators with appropriate experience, skills and training. Emphasis should be placed on the multidisciplinary heart team approach." Criteria for the selection of investigation sites and clinical investigators are listed (7.4.5) (see Supplementary Table).

Two standards on cardiovascular implants (7198 and 17137) do not provide guidance whether or how to identify a study population representative for the target population. It is only stated that inclusion and exclusion criteria for the patient selection should be clearly identified. The remaining three standards on cardiovascular implants (25539-1 and -2; 12417-1) state that "the criteria shall specify the target population (i.e. those for whom the implant is intended) and the accessible population (i.e. those who agree and are able to participate fully in the study)."

Intervention: ISO 14155 states that the CIP must contain a detailed description of the investigational device and the specific medical or surgical procedure involved in the use of the device (A.2): It should describe any materials that will be in contact with body fluids and tissues, the model type, and software version and accessories, "to permit full identification". A "summary of the necessary training and experience needed to use the investigational device based on risk assessment", and a description of the traceability of the device after the investigation, are also required. The investigator's brochure should give further details such as a description of the components of the device and any materials used, and information about its mechanism of action (B.2).

In all device-specific standards, there is no stated requirement for the CIP to define and describe the intervention (i.e. the investigational device with related procedures and co-treatments). ISO 17137 refers generally to ISO 14 155 and 12417-1 for the CIP and the final report. In the other eight standards, under the clauses on "data acquisition" or "clinical data requirements", a section called "procedural" or "operative data" is provided where relevant data for a description of the device, the procedure and relevant medications are listed, but a clear definition of the intervention for the CI is not demanded.

Comparator: According to ISO 14155, the "results of the clinical evaluation and the risk assessment […] shall also serve to justify the choice of control group(s) and if applicable, comparator(s) […]" (6.3). "Absence of control(s) shall be justified" (A.6.1). The same information as for the investigational device shall also be provided for the comparator (A.2). ISO 14155 does not further specify the choice of controls.

The benefit-risk analysis of the risk management process is used to determine if the residual risk is outweighed by the expected benefits of the intended use of the medical device (ISO 14971). The guidance to benefit-risk analysis in ISO 24971 states that an "important consideration is whether an anticipated benefit can be achieved using alternative solutions without that risk or with smaller risk. This involves comparing the residual risk for the manufacturer's medical device with the residual risk for similar medical devices."

The four standards on heart valves ([59], [61], [62], [63]) state that if a comparable device is on the market, the study control "may be the comparable device or another active comparator". One of the reasons listed as a rationale for conducting an RCT is that ethical considerations may require a head-to-head comparison with alternative treatments or standard of care (7.4.1). ([59],[62], [63]) Among these standards, ISO 5840-2 distinguishes between novel devices including devices with characteristics that have never been evaluated before, and devices with established designs. For the latter the recommended method is to use objective performance criteria as the control for adverse events (see Supplement Table).

ISO 17137 directly recommends an RCT with an existing device as control, indicating that the control device should represent the standard of care: "Control devices should be contemporary non-absorbable devices, unless absorbable devices have been established as the preferred mode of treatment in the intended clinical application."

The four remaining standards on cardiovascular implants ([57], [58], [60], [65]) only demand a rationale for the choice of control in the requirements for the final report of the CI, and a justification if a control group is not used. No further recommendations for the choice of the control group are made.

Outcomes: ISO 14155 describes primary and secondary endpoints of a clinical investigation as:

- "<**primary**> principal indicator(s) used for providing the evidence for clinical performance […], effectiveness […] or safety in a clinical investigation […]", and
- "<**secondary**> indicator(s) used for assessing the secondary objectives […] of a clinical investigation [...]" (3.22; 3.23).

It is stated that "the primary endpoint shall be appropriate for the investigational device and should be clinically relevant." A note clarifies that a "**Composite** endpoint is a pre-specified combination of more than one endpoint and can be used cautiously by including only components that have relatively equal clinical importance, frequency, and anticipated response to the presumed mechanism of action" (A6.1c).

The five standards on cardiovascular implants ([57], [58], [60], [64], [65]) state that the purpose of the clinical investigation or evaluation is to assess the safety and effectiveness of the device under consideration (see Supplementary Table Objective). They also provide specific aims which operationalize effectiveness and safety, regarding categories of outcomes relevant for the device under consideration. The four standards on heart valves ([59], [61], [62], [63]) state similarly that "For clinical investigations to serve as a basis for market approval, there should be sufficient data to support safety and effectiveness." (See Supplementary Table)

Thus, all nine standards require that both safety and effectiveness endpoints have to be specified prospectively in the CIP/study protocol (see sections on "Protocol considerations", "Clinical investigation plan", "Study considerations", respectively).

The four standards on heart valves ([59], [61], [62], [63]) mention in their three normative annexes on clinical endpoints for AE (Appendices G, J, Q) and their two annexes on clinical safety and effectiveness endpoints (L normative, S informative), that composite endpoints which combine safety and effectiveness should be avoided "because the individual components of safety and effectiveness may move in opposite directions" (G8.1, J8.1, Q8.1, S2.5). Annex L of ISO 5840-1 recommends not to use a single composite clinical safety and performance or effectiveness endpoint, but if one is used then the individual components of the composite primary endpoint should be assessed as secondary endpoints (L4). Three ([57], [64], [65]) of the five standards on cardiovascular implants ([57], [58], [60], [64], [65]) do not give recommendations on composite endpoints. ISO 25539-1 and 25539-2 do not give recommendations on the use of composite endpoints but suggest using the single components of composite endpoints as secondary endpoints (8.7.3).

Safety outcomes

ISO 14155 defines **safety** as "freedom from unacceptable risk" (3.26), and risk as "combination of the probability of occurrence of harm […] and the severity of that harm" (3.18). Harm is defined as" injury or damage to the health of people, or damage to property or the environment" (3.3). It is not explicitly mentioned in ISO 14155, but endpoints to assess safety are usually adverse events.

ISO 14155 defines **adverse event** (**AE**) as "untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects […], users or other persons, whether or not related to the investigational medical device […] and whether anticipated or unanticipated." This definition is the same as in the MDR of the European Union Article 2(57). Three notes further clarify that the definition also applies to the comparator in the investigation, that procedure-related events are included, and that for users or other persons this definition is restricted to events related to the use of investigational medical devices or comparators (3.2).

Further the "**adverse device effect** (**ADE**)" is defined as "adverse event related to the use of an investigational medical device" and clarifies in three notes that AE "resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction […] of the investigational medical device" […] and "any event resulting from user error or from intentional misuse of the investigational device" are included and that this definition also includes comparator devices (3.1).

Serious AE (**SAE**) is defined as "adverse event[s] that led to any of the following:

a) death,

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

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, [or]

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

A note clarifies that a "planned hospitalization for a pre-existing condition, or a procedure required by the CIP […], without serious deterioration in health, is not considered a serious adverse event" (3.45).

A **serious ADE** (**SADE**) is defined as "an ADE that has resulted in any of the consequences characteristic of a SAE" (3.44). A distinction is made between anticipated and unanticipated SADE: an anticipated SADE has been already identified by its nature, incidence, severity or outcome in the risk assessment. An unanticipated SADE has not been identified in the current risk assessment (3.51).

Annex F of ISO 14155 summarizes these categories of AE in Table F1 in appendix F (see Table 8). It provides a flow chart for AE and ADE with questions to answer for classification, in Figure F1 and F2 in the ISO document (not shown). A classification for device deficiencies not leading to an AE (with SADE and without SADE potential) is also provided.

Table 8. Categorization of adverse events according to Annex F of ISO 14155

<table>
<tr><th>Adverse events</th><th>Non-device-related</th><th colspan="2">Device- or investigational procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse event (AE)[1]</td><td colspan="2">Adverse device effect (ADE)[3]</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious adverse event (SAE)[2]</td><td colspan="2">Serious adverse device effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated serious adverse device effect (ASADE)[3]</td><td>Unanticipated serious adverse device effect (USADE)</td></tr>
<tr><td colspan="4">[1] Includes all categories, [2] Includes all categories that are serious, [3] Includes all categories that are related to the device or the investigational procedure.</td></tr>
</table>

During the CI, all AE shall be documented in a timely manner (7.4.2). The sponsor is responsible for evaluating safety and for classifying AE (seriousness, relationship to the investigational device; and procedures required by the CIP). If the sponsor and principal investigator disagree, both opinions shall be communicated to the ethical committee, regulatory authorities, and the data monitoring committee. Classification of AE and safety evaluation can be performed by an independent clinical events committee, to mitigate bias and financial interest of conflict (9.2.5). The principal investigator also has to record and report AE and device deficiencies and classify them (10.8).

The classification of AE and ADE in ISO 14155 is valid for all device-specific standards, since they require compliance with its requirements for CI. The four heart valve standards ([59], [61], [62], [63]) provide a normative annex dedicated to adverse event classification during clinical investigation for the specific device or relate directly to such an annex [61].

ISO 5840-1 contains a normative annex (L) specifying safety and effectiveness endpoints, which lists five mortality endpoints that shall be reported:

- all-cause mortality;
- cardiovascular mortality;
- non-cardiovascular mortality;
- procedural mortality (30 d from procedure or discharge from the hospital, whichever is longer);
- device related mortality".

It refers to further AE in annexes G and J of ISO 5840-3 and ISO 5840-2, respectively. In them and in annex Q of ISO 5910, between 45 and 50 examples of AE are listed for the specific devices. It is demanded that the most recent definitions of specific adverse events shall be applied for data collected on events occurring during the device-related procedure and the peri-procedural period. In addition to the general principles for classifying AE and ADE given in ISO 14155, a scheme is described with four categories for defining any causal relationship between the AE and the device, the procedure, the patient's disease, or other causes. Further it is explicitly demanded that "an independent, multi-disciplinary committee of qualified experts shall adjudicate causality to assign the specific cause of an adverse event. Formal adjudication of adverse events is intended to manage the ambiguity and bias in assigning causality" (G7, J7, Q7). ISO 5910 contains an informative Annex S that lists 31 single safety endpoints and also effectiveness endpoints.

Three of the standards on cardiovascular implants (58, 60, 65) provide informative annexes with definitions or descriptions of possible clinical effects resulting from failure of the device and of consequences for its function. Regarding the other standards, ISO 7198 mentions no specific AE or ADE. ISO 17137 points out that late AE may occur with absorbable stents, but no specific AE is described.

Effectiveness outcomes

ISO 14155 does not categorize performance or effectiveness outcomes. ISO 14971 characterizes categories of outcomes that are relevant to assess benefit:

> "**Benefits** can include positive impact on clinical outcome, the patient's quality of life, outcomes related to diagnosis, positive impact from diagnostic devices on clinical outcomes, or positive impact on public health" (3.2).

Basically, all nine device-specific standards state that effectiveness endpoints should be derived from the research questions (see Supplementary Table).

ISO 5840-1 includes effectiveness endpoints in its normative annex L, and the other two standards of the ISO 5840 series refer to it (7.4.3). Firstly, it explains the term 'effectiveness' and the principles to assess it in the context of cardiovascular valve prostheses:

> "**Effectiveness** means that the device itself is conferring some clinical benefit but there is a spectrum of effectiveness which shall be quantified. The assessment of effectiveness shall incorporate an assessment of device performance because it is possible for patients to claim improved functional status due to concomitant changes in medication, a placebo effect or because they do not wish to disappoint their physician. All assessments of effectiveness should be based on physical examination with access to imaging, hemodynamic and other relevant data. All assessments should be carried out by independent, unconflicted physicians, where possible. In order to be considered effective, the device shall perform as intended without deleterious hemodynamic consequences, e.g. significant regurgitation" (L2.3).

Then 18 endpoints are listed, relating to immediate outcome, outcome at 30 days, and outcome during long-term follow-up. A definition of heart failure hospitalization is provided.

Annex S of ISO 5910 also includes both safety and effectiveness endpoints, but it is only informative. It is stated in the introduction that the endpoints "should reflect patient centric benefit such as living longer, feeling better or functioning better" (S1), but further that "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 standard lists 18 effectiveness endpoints that should be considered. In order to "support the determination that any observed clinical benefit was due to the device intervention", it is recommended that "continued evidence of device success should be present at the time of primary effectiveness endpoint assessment" (S2.3). The same definition of heart failure hospitalization is given as in annex L of ISO 5840-1.

The five standards on cardiovascular implants ([57], [58], [60], [64], [65]) list several categories of effectiveness endpoints, such as ability to access the target location etc., under "specific aims" of the study (see Supplementary Table). In the section on data acquisition, four of these standards ([57], [58], [60], [65]) also list effectiveness endpoints. ISO 17137 refers to ISO 12417-1. ISO 25539-1 provides a list of possible secondary endpoints including effectiveness endpoints.

All device-specific standards require that effectiveness and safety endpoints, and the time points to assess them, are specified in advance in the CIP/study protocol, and that it should also provide definitions of failure or success (see Supplementary Table).

The four standards on heart valves ([59], [61], [62], [63]) indicate that standardized endpoints should be used to guarantee the comparability of the evidence from different studies. "The ability to compare clinical investigations and to create useful observational registries requires the use of consensus definitions of endpoint components" (ISO 5840-1 Annex L.1). The five standards on cardiovascular implants do not mention standardized or agreed endpoints.

4.3.7 Statistical methods

According to ISO 14155, the requirements for statistical methods to be used for a clinical investigation derive from its optimal design, as identified by the clinical evaluation and risk assessment. Elements of statistical methods are specified in more detail in section A.7 of annex A, which lists the necessary content of the CIP. Paragraphs in A.7 a) to q) contain 17 items of "statistical design and analysis" that should be described and justified.

Justification of the sample size and its calculation should take into account all clinical outcome data, the effect size, assumptions of expected outcomes across treatment groups, adjustments due to pre-planned interim analyses, randomization allocation ratio, and the expected drop-out rate, as well as the detectable effect size and the non-inferiority margin (which should be smaller). All statistical parameters and methods used to calculate the sample size or the non-inferiority margin should be clearly provided (A.7e).

Other items listed regarding statistical analysis are the approach to analyze the data of the study population "and procedures that take into account all the data" (A.7a), descriptive statistics (A.7.b), and the management and handling of missing data including sensitivity analyses of different methods (A.7. m, n).

Regarding the analysis and handling of **statistical uncertainty**, i.e., random error, the overall statistical testing strategy, procedures to calculate the confidence intervals, and the significance level and statistical power for the primary endpoint, have to be described. A two-sided significance level of alpha of 0.05, or a one-sided significance level of alpha 0.025 and a statistical power between 0.8 and 1, does not have to be justified. Other values have to be justified (A.7 c, d). Interim analysis and criteria for termination of the clinical investigation on statistical grounds, as well as procedures for multiplicity control and adjustment of the alpha- level, have to be provided (A.7 h, k). Procedures for the management of systematic errors (bias) by design and analysis should be considered and justified (A.7 i, j), as well as the management of potential imbalances in the number of study participants in multicenter studies (A.7p), and "a strategy for pooling data" (A.7.q). The learning curve of a single user has to be addressed by providing a rationale for the number of procedures to be performed and how these data should be analyzed.

The four standards on heart valve devices ([59], [61], [62], [63]) state for the CIP that "the study design shall include a pre-specified statistical analysis plan and success criteria", and that the manufacturer is responsible for selecting and justifying the statistical methodology. "The size, scope, and design of the clinical investigation shall be based on:

a) the intended use of the device;
b) the results of the risk analysis;
c) the measures that will be evaluated; and
d) the expected clinical outcomes" (7.4.2).

For pivotal studies the four heart valve standards give detailed guidance on the sample size and its calculation. In addition to repeating the requirements on alpha-level and power of ISO 14155 for calculation of the minimum sample size, it is mentioned that "the standard of care and available safety

and performance or effectiveness data (including post-market or published data) on relevant therapies with similar intended use" should be taken into account for the calculation (7.4.6).

For all heart valve devices, **a minimum of 150 patients** in each valve position should be studied for at least one year, and

> "in addition, at least **400-patient years of data** are required in the pre-market setting to assess late adverse events (e.g. thromboembolism, device thrombosis, hemorrhage, and infective endocarditis) for heart valve substitutes implanted by transcatheter techniques and for cardiac valve repair devices ([59], [63]). The 400 patient-years criterion can be met by further pre-market follow-up of the 150 patients beyond 1-year or by enrolment of additional patients."

The recommendation to collect 400-patient years of data is based upon using a null hypothesis that the actual adverse event rate is twice the event rate currently accepted for similar devices, with probabilities of a one-sided type one error of 5 % and of a type 2 error of 20 % (7.4.6). For assumptions on accepted event rates, a reference is provided, and a table shows the relationship between expected AE rates and sample size. The expected AE rates range from 1.0 to 10.0% per year, leading to a range of patient-years necessary between 972 and 97.

For surgically implanted heart valve substitutes that are new but based on established device designs, the recommended method for the evaluation of AE is the use of **objective performance criteria** (**OPC)** (ISO 5840-2 7.4.6.2). In the normative annex I that provides guidance on this method, a minimum of 800 patient-years is required for a valve implanted in a single position, due to the low AE rates that have been identified by analysis of safety and effectiveness data submitted by prior manufacturers in pursuit of premarket approval, combined with an analysis of recent literature (ISO 5840-2 Annex I).

Nonetheless, in the main text it is stated that "in niche indications, rare diseases or less common patient populations […] a smaller sample size and shorter premarket follow-up durations may apply but shall be defined and justified based on disease prevalence, unmet clinical needs and risk/benefit considerations" (7.4.6.2). Similarly in ISO 5910, a smaller sample size may be justified if the population to be studied is not of acceptable risk to allow surgery to be undertaken. This must be based on a robust statistical analysis which takes into consideration the anticipated risk-benefit profile. "Departures from the recommended 400 patient-years sample size shall be adequately justified" (ISO 5910 7.4.6).

The five standards on cardiovascular implants ([57], [58], [60], [64], [65]) demand a statistical justification of the sample size. ISO 12417-1 and ISO 17137 also require that loss to follow-up is considered in the calculation. ISO 7198 demands that no investigational site should enroll more than 50 percent of the study subjects, while ISO 25539-1 and -2 recommend that no more than 35% of the study subjects are enrolled at one investigational site.

While the standards on heart valves ([59], [61], [62], [63]) recommend including information on all subjects for whom implantation was planned, and to perform an **intention-to-treat** analysis and additional analyses on those subjects who received the implant, ISO 12417-1 and ISO 17137 state that only all patients "treated with either the test or control device shall be recorded and reported". This excludes an intention-to-treat analysis. In the remaining three standards ([57], [58], [60]), it is unclear

which type of analyses should be performed. It is stated only that “All patients enrolled in the study, including those excluded from the primary endpoint analyses, shall be recorded and reported” (10.1.3, 8.7.3).

4.3.8 Contextual factors and learning curve

The implications of learning curves for trial design and analysis are considered in ISO 14155 as part of the risk management: “Where the risk management report’s conclusions require training on the investigational device, consideration should be made by the sponsor about the extent of the training […]” (6.2.2). The issue should be addressed in the “Statistical design and analysis” section of the CIP. Characteristics of healthcare providers and investigational sites are not part of eligibility criteria to be considered or reported, in the design and analysis of the clinical investigation.

In the four standards on devices for heart valves, a detailed description is provided on requirements for investigational sites and investigators for pivotal CI ([59], [62], [63]), or else reference is made to them (61). “Clinical investigations shall be conducted in institutions with appropriate facilities, case-load and case-mix and by investigators with appropriate experience, skills and training.” Investigators and institutions should be representative for the intended patient and user populations. “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” (7.4.5). Investigators should have adequate expertise and experience, and potential conflicts of interests should be managed (7.4.5). The five standards on cardiovascular implants do not provide recommendations for the selection of investigational sites or investigators or on the consideration of learning curves.

4.3.9 Reporting of clinical investigations

Annexes A to D of ISO 14155 provide four templates for reporting the essential parts of a clinical investigation. Annex A on the content of the **clinical investigation plan** (CIP) and Annex B on the content of the **investigator’s brochure** (IB) are important for the preparation and planning of a CI. Both annexes are normative and describe which contents must be included as a minimum in the respective documents. Annex C for developing **case report forms** (CRFs) is informative; their role is:

> “to implement the CIP, to facilitate subject observation and to record subject and investigational device data during the clinical investigation according to the CIP. They can exist as printed, optical, or electronic documents and can be organized into a separate section for each subject. The CRFs should reflect the CIP and take account of the nature of the investigational device” (A C.1).

Annex D is normative and “specifies the contents of the clinical investigation report that describes the design, conduct, statistical analysis, and results of a clinical investigation.” The format in Annex D may also be used in interim, progress or annual reports (D.1).

Annex A for the CIP comprises nine pages and all the topics listed in this annex shall be included in the CIP. We have already presented relevant parts of it in the previous sections. Annex A contains 18 sections (see Supplementary Table). The most important sections for study design are:

- A.3 Justification for the design of the clinical investigation,
- A.4 Benefits and risks of the investigational device, clinical procedure, and clinical investigation,
- A.5 Objectives and hypotheses of the clinical investigation,
- A.6 Design of the clinical investigation,
- A.7 Statistical design and analysis,
- A.8 Data management,
- A.14 Adverse events, adverse device effects, and device deficiencies,
- A.16 Suspension or premature termination of the clinical investigation, and
- A.17 Publication policy.

According to section A.3, the justification for the study design shall comprise an evaluation of results of the relevant pre-clinical testing and prior clinical investigations carried out to justify the use of the investigational device in humans, an evaluation of clinical data relevant to the proposed CI, and a description of the development stage.

In A.4 issues to be reported are anticipated benefits and adverse effects, further elements from the risk analysis related to the clinical procedures and clinical investigation, and a rationale for the benefit-risk ratio. In sections A.5, A.6, A.7 and A.14 a description has to be presented of study objectives and hypotheses, their operationalization by determining the study population, the intervention and comparators, and the endpoints and methods for statistical analysis. Scientific justifications have to be provided for the study type (A.3), effect sizes, non-inferiority margins or equivalence margins, comparators, absence of comparators, number of investigational devices, and for all 17 items listed in the section on statistical design and analysis. A rationale has to be provided for non-reportable adverse events (A.14) (see Supplementary Table).

According to section 6.5 of Annex B, the purpose of the **investigator's brochure** (IB) is:

> "to provide the principal investigator and the investigation site team with sufficient safety or performance data from pre-clinical investigations or clinical investigations to justify human exposure to the investigational device specified in the CIP. The IB shall be updated throughout the course of the clinical investigation as significant new information becomes available (e.g. a significant change in risk)."

The IB "shall contain, as a minimum, all topics listed in this annex" (B.1.1), and "the information shall be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased benefit-risk analysis of the appropriateness of the proposed clinical investigation" (B.1.1).

Section B.2 lists the content for information about the investigational device (see Supplementary Table). Section B.3 lists ten items which shall be included in the summary on preclinical testing of the MD. Section B.4 demands a "summary of relevant previous clinical experience with the investigational

device and with medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device", and "analysis of adverse device effects and any history of modification or recall", without further specification. B.5 on the risk management of the investigational device lists as items to describe a" summary of the benefit-risk analysis including identification of residual risks" and "contra-indications and warnings for the investigational device." Section B.6 shall contain regulatory references such as lists of international standards and statements of conformity with national regulations.

The main goal of informative annex C is to facilitate valid data management by using standardized case report forms. It contains a list of steps for a CI, such as screening, base-line visit, follow-up visits or safety reporting etc., for which a CRF may be helpful. Fifteen issues with five sub-issues are listed. We do not report this further here, because the other issues are not relevant for the design of CI.

The normative Annex D "specifies the contents of the clinical investigation report that describes the design, conduct, statistical analysis, and results of a clinical investigation" (D.1). Parts D.5 to D.8 are important for trial design and results. D.5 states that the introduction shall contain "a brief statement placing the clinical investigation in the context of the development of the investigational device, and relating the critical features of the clinical investigation (e.g. objectives and hypotheses, target population, treatment and follow-up duration) to that development". Guidelines that were followed in the development of the CIP or agreements with regulators should be described. In section D.6, the investigational device and methods used shall be described. Section D6.1 contains instructions for the investigational device, the description of the device and its intended use, in addition to previous intended uses or indications for use. Any changes to the investigational device during the CI shall be described, and six items are mentioned explicitly. D.6.2 contains a description of a summary of the CIP. All subsequent amendments shall be provided, with a rationale for each. For the **CIP summary** the following items are listed:

- the CI objective,
- the CI design including type of CI,
- endpoints and control group,
- the ethical considerations,
- the data quality assurance,
- the subject population including inclusion/exclusion criteria and sample size,
- the treatment and treatment allocation schedule,
- any concomitant medications/treatments,
- the duration of follow-up,
- the statistical design, analysis, and justifications including the CI hypothesis or pass/fail criteria, a sample size calculation, statistical analysis methods, and interim analyses.

D.7 describes elements which the **results section** shall include:

- the start and completion or suspension date of the CI,
- the disposition of subjects; numbers screened, randomized, and received therapy,
- the disposition of investigational devices,
- the subject demographics and other relevant baseline characteristics,

- CIP compliance, an analysis with rationale and justifications, which includes all clinical performance, effectiveness or safety analyses provided for in the CIP,
- results of components of composite endpoints, when used,
- a summary of all adverse events and adverse device effects, including a discussion of the severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure,
- a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any corrective actions taken during the clinical investigation,
- any needed subgroup analyses for special populations,
- an accountability of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects not passing screening tests, lost to follow-up, and withdrawn or discontinued from the clinical investigation and the reason,
- clear distinctions between primary analyses, other pre-specified analyses, and additional analyses, [and]
- listings of deaths and reasons for deaths.

D.8 contains a description of the elements of the discussion and the overall conclusions. “The conclusions shall be based on the intended use and target population of the investigational device”. **Reporting of the conclusions** shall include:

- the clinical performance, effectiveness, or safety results and any other endpoints,
- an assessment of benefits and risks,
- a discussion of the clinical relevance and importance of the results in the light of other existing data,
- any specific benefits or special precautions required for individual subjects or groups considered to be at risk,
- any implications for the conduct of future clinical investigations,
- any limitations of the clinical investigation e. g. selection, retention, and compliance of subjects, selection and adherence of investigation sites and users, and investigation site environment type(s), [and]
- bias introduced by missing observations, by confounders and by selection of subjects or sites.

The remaining sections contain guidance on reporting on ethical issues of the CI (D.10), the administrative structure (D.11), and annexes to the report (D.13) including all documents in length that are reported in the CIR (see Supplementary Table).

The four device-specific ISO standards on heart valves (ISO 5840-1, -2, -3, 5910) state in their sections on CI that “The Clinical Investigation Report shall comply with ISO 14155” ([59], [61], [62], [63]), while ISO 5840-1 refers additionally to ISO 5840-2 and -3. Three of these standards ([59], [62], [63]) give additional requirements for reporting: For randomized studies, an intention-to-treat analysis is required as the ‘base case’ analysis, and in addition a per-protocol analysis is demanded. The annexes describe more endpoints that have to be considered for the CI, that are specific for the respective cardiac valve technologies. In addition to ISO 14155, they demand that “a justification shall be provided for those who were randomized to but did not receive an implant”.

Registration of CI is required in publicly available databases, and it should include the disclosure of negative and positive results. Several paragraphs in ISO 14155, but not Annex D on the CIR, demand study registration and reporting of results (5.4, 5.8.4, 8.4, A.17). The percentage of follow-up completeness should be given, with reasons for losses. Other requirements are more specific to heart valve studies:

> "if investigations have been conducted during follow-up (e.g. echocardiography), the percentage of patients receiving the investigation and how they were selected shall be stated", and "efforts shall be made to ascertain the cause of death, including contact with local physicians if the patient died elsewhere, obtaining details of any investigations performed shortly before death, and autopsy data and explant data if available. Reliance on national healthcare databases to simply record that death has occurred is insufficient. A high percentage of patients with unknown cause of death raises suspicion of device-related deaths."

Two of the five ISO standards on cardiovascular implants, ISO 7198 and ISO 12417-1 ([57], [65]) state directly that the CI shall be carried out using the principles of ISO 14155, whereas the other three standards (ISO 17137 and ISO 25539-1, -2) ([58], [60], [64]) also allow equivalent publications.

ISO 17137 states "In addition to the final clinical investigation reporting of specifications outlined in ISO 14155 and ISO 12417-1, a rationale shall be provided for the selection of patient follow-up intervals and for the selection of assessments at each time point based on the degradation profile of the implant".

ISO 12417-1 although referring to ISO 14155, provides a list with content that shall be included as a minimum in the final report (7.3.5). This list contains elements which duplicate those in ISO 14155, such as providing the study protocol and giving justifications for the study size, the choice of control, the statistical analyses employed, any deviations from the protocol, and patient accountability. and others of which is unclear whether "summary of patients not completing the study" might be covered in the formulation in ISO 14155 "an accountability of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects". The summary in ISO 12417-1 might also contain patient characteristics, but this is not mentioned explicitly. Other issues listed already in ISO 14155 such as "summary of reportable clinical events" are specified in more detail and device specific: the timing of the event has to be indicated in relation to the procedure (procedural, peri-procedural, follow-up interval). Further, more device-specific issues are listed in items 6 to 12 (see Supplementary Table), such as summary of vascular device-drug combination product (VDDCP) performance over time (e.g. VDDCP migration, patency, percentage of diameter stenosis, drug combination product integrity, unanticipated alterations in shape).

The three ISO standards 7198, 25539-1 and -2 share the same list of items to report as ISO 14155, for example regarding the reporting of the study protocol. There are also some references to device-specific endpoints, such as technical success and procedural success, and there are some modifications of items in the results section h) (see Supplementary Table), for example concerning relevant disease-specific risk factors.

4.3.10 Summary and discussion

We identified 12 ISO standards providing recommendations on the study design of pivotal clinical investigations of medical devices: ISO 14155 on good clinical practice for clinical devices, and ISO 14971 and ISO 24971 on the application of risk management to medical devices, are general standards that apply to all risk classes of medical devices; while the other ISO standards cover high-risk devices in the field of cardiovascular disease, that were a focus of the CORE-MD project. The specific objective of this review was to identify guidance on methodologies for clinical investigations and trials of high-risk medical devices.

4.3.10.1 ISO 14155

The general standard ISO 14155 on good clinical practice for clinical investigations of medical devices covers non-IVD devices of all risk classes but it does not provide a hierarchy of levels of evidence related to study designs for performing clinical investigations. The definition of design types used in ISO 14155, as "exploratory, confirmatory or observational", is also neutral regarding evidence levels.

From the definition of a confirmatory clinical investigation in Annex I 4.3, it can be deduced that the study has to be at least an interventional study, "adequately controlled", with pre-specified hypotheses of the primary endpoint(s), and with sound confirmative statistical testing (Annex I 4.3). To justify and specify the optimal study type and design of a CI, a clinical evaluation and the risk assessment has to be performed according to ISO 14971 and ISO 24971. "The clinical evaluation shall also help to identify relevant endpoints and confounding factors to be taken into consideration and serve to justify the choice of control group(s) and if applicable, comparator(s), the use of randomization or blinding, and other methods to minimize bias" (6.3).

The principles to be considered when choosing a study design – clinical relevance, scientific validity, and bias minimization – are very general and if not operationalized in more detail insufficient to judge or compare different study designs with regard to their validity. In clinical epidemiology and evidence-based medicine, non-randomized studies are usually considered prone to bias to such an extent that only randomized studies are deemed appropriate to provide evidence of clinical effectiveness (see Cochrane Handbook) [66].

Whether there is a need for a CI is also stated in very general terms. According to ISO 14971 and ISO 24971, it is determined by the risk analysis that has to be performed when planning a CI. ISO 14155 demands an "objective review of published and unpublished medical and scientific data" but that is not mentioned as a routine requirement in ISO 14971 or ISO 24971 and it is unclear whether an "objective review" corresponds to the term "systematic review" as defined by evidence-based medicine [66].

ISO 14155 demands that general elements of study design such as objectives, study hypotheses, definition of study success, study population, investigational device, controls or absence of controls, study endpoints, the elements of statistical analysis with specification of false positive (type I) and false negative (type II) error rates, are all prespecified and justified. The annexes have detailed

descriptions for the CIP, the IB and the clinical investigation report to determine what is considered their minimum content.

The skills and training of providers and the volume of interventions in hospitals influence success and complication rates [67]. In section 6.8 on the selection of investigation sites, ISO 14155 demands that the sponsor "shall identify criteria necessary for the successful conduct of the clinical investigation prior to start of the site qualification process, including the facilities required at the clinical investigation site, principal investigator's qualification and the type of environment", and "the rationale for selecting an investigation site shall be documented". An investigation site selection report has to be prepared prior to the CI. For the findings of a study to be widely applicable, it is stated also that "the investigation site's facilities should be similar to the facilities required for the intended use of the investigational device(s)".

Since both positive and negative outcomes of an intervention depend on the provider and the institution where the intervention takes place, in our opinion this special feature of medical devices and in particular of high-risk medical devices such as implants should be directly integrated into recommendations on the description of the study design in the CIP. At least for confirmatory studies, inclusion criteria for institutions should be defined and the representativeness of intended providers and facilities should be evaluated, to enable future judgments about the applicability of study findings for a device to the population for its intended use.

The role of ISO 14971/24971 for the design of clinical investigations is mainly to provide a systematic method for analyzing risk and for deciding whether residual risk is outweighed by the benefits expected from the intended use of the medical device. These standards may influence the choice of study design in a CI, but only indirectly through measures that have to be taken to control residual risks, and so we will not consider them further here.

4.3.10.2 Device-specific ISO standards

We found nine device-specific standards relevant to the medical fields which we investigated – four on implants for heart valves, and five on other cardiovascular implants (all summarized in Table 9). They refer to ISO 14155 and some other device-specific ISO standards, while also providing their own device-specific guidance on study design.

Eight standards recommend a CI for all new devices or for expanded use of a device. One uses the formulation "[devices] incorporating design characteristics for which the safety and effectiveness have not been previously demonstrated" [65]. The standards on heart valves ([59], [61], [62], [63]) demand a justification when no CI is performed in the case of any device that is a modification of a device that has already been evaluated. Three of the five standards on cardiovascular implants ([57], [58], [60]) identify the need for a CI for any devices with "significant changes", or else a justification for not performing a CI. The justification has to be based on the risk analysis.

The four standards on heart valves and one of the standards on cardiovascular implants [64] recommend an RCT for the CI of a new device, whereas the other four standards on cardiovascular implants recommend multi-center trials with a control group, or else a justification for no control group. Multi-center trials should recruit participants from at least three sites. ISO 5840-2 recommends

incorporating OPC in the study design for established devices. Explanations are given in a normative annex on the sample size and data necessary for applying OPC, which are the rates of valve-related complications averaged across all successful submissions by manufacturers for premarket approval, derived from a systematic review and meta-analysis. Regarding general design issues, the PICO specifications are especially relevant for device-specific recommendations. The degree of detail and elaboration of recommendations is different for the four elements and also between standards.

The standards for heart valves are all structured according to the same scheme, as are the standards for cardiovascular implants but using a different structure. All device-specific standards provide detailed recommendations for primary and secondary safety and effectiveness endpoints, but here too they use different formats. Some use annexes to describe and define single and composite endpoints, whereas other standards list these under “protocol considerations” or “data acquisition”.

A greater difference exists in the extent and content of recommendations for defining the **study population**. The standards for heart valves emphasize the need for the study population to be representative, and they list inclusion criteria not only for the study population but also for investigational sites and clinical investigators. They also recommend documentation of prognostic factors, and justification of any differences between the study population and the intended target population. In comparison, the other standards on cardiovascular implants recommend only in general terms that inclusion and exclusion criteria shall be specified, but without giving further detail.

The **implantation** of a high-risk medical device is often a complex intervention, and the device can consist of several different components that may be applied using a variety of procedures or accompanied by different co-therapies. Thus, a comprehensive description of the intervention should be an important part of a study protocol or publication, to allow the physician to judge whether the results of the study are transferable to her or his setting. Further, this information is also necessary for aggregation of evidence for a device or a class of devices in systematic reviews and meta-analyses, which will be needed for the clinical evaluation in the preparation of clinical investigations. The ISO standards do not give a recommendation to describe the entire intervention clearly in the CIP (the device, procedures for its application, and any co-therapy), but a description of all components of the intervention should be included.

Looking at the recommendations for the choice of **the control group**, a similar picture emerges. While the standards on heart valves and one of the standards on cardiovascular implants (ISO 17137) make concrete recommendations (for an active control group receiving comparable ‘standard of care’ devices or other relevant treatments, when investigating new devices, or for OPC when evaluating established devices) the remaining four standards for cardiovascular implants repeat only the general recommendations by ISO 14155 without any specification. Also, regarding the recommendations for the statistical analysis of CI, the ISO standards for cardiovascular implants remain at the general level of the recommendations of ISO 14155, except for the recommendation not to enroll more than 50% of the study population at one site, while the ISO standards for heart valves contain specific sample size calculations and recommendations, and concrete values for acceptable OPC.

Overall, the sections in device-specific ISO standards on recommendations for study design are heterogenous in structure and variable in content, with differences that can hardly be explained by

differences between the devices. For example, RCTs are recommended for devices with new characteristics in five of the standards, while unspecified multi-center studies with at least three sites and a control group are recommended in the other standards. A uniform structure of the outline of the section on CI in device-specific ISO standards might help to support a more standardized consideration of device-specific issues in trial design. Heterogenous recommendations that are not based on differences between devices should be avoided. Given the important role that harmonized standards play for conformity assessment and CE certification in the EU, as well as in other jurisdictions, this may contribute to uneven conditions for market approval between different types of devices. More accessible guidance on how to develop recommendations in ISO standards might be helpful.

Table 9. Recommendations on study design from nine device-specific ISO standards

	Heart valves				Stents, grafts, patches				
Design recommendations	**ISO 5840-1 2021**	**ISO 5840-2 2021**	**ISO 5840-3 2021**	**ISO 5190 2018**	**ISO 7198 2016**	**ISO 12417-1 2021**	**ISO 17137 2021**	**ISO 25539-1 2017**	**ISO 25539-2 2020**
Description study types	None				FDA classification	None	None	FDA classify-cation	Use appropriate terms[1]
When is a clinical investigation needed?	For new devices or for expanded indications								
	For device modifications, justification if no CI.				For significant changes, justification if no CI.	None	None	For significant changes, justification if no CI.	
Choice of study types	RCT for pivotal CI, but depending on purpose, novel vs. modification or well-established technology. ISO 5849-2 5840-2 recommends objective performance criterion (OPC) comparison for new devices based on established device designs, with sample size calculation in annex I.				Controlled multi-center trials with at least 3 sites, justification if no control.		Sufficiently powered RCT	Controlled multi-center trials with at least 3 sites, justification if no control.	
General design principles	The clinical investigation program shall be designed to provide substantial evidence of acceptable safety and effectiveness to support the intended labelling for the device.				Purpose of CI is to assess the safety and effectiveness. Safety and effectiveness have to be operationalized into more specific aims.				
	The size, scope, and design of the clinical investigation shall be based on: a) the intended use of the device; b) the results of the risk analysis; c) the measures that will be evaluated; d) the expected clinical outcomes.				CI is not intended to demonstrate long-term performance.	-	-	CI is not intended to demonstrate long-term performance.	

Heart valves					Stents, grafts, patches				
Design recommendations	**ISO 5840-1 2021**	**ISO 5840-2 2021**	**ISO 5840-3 2021**	**ISO 5190 2018**	**ISO 7198 2016**	**ISO 12417-1 2021**	**ISO 17137 2021**	**ISO 25539-1 2017**	**ISO 25539-2 2020**
	Justification needed if the pivotal study is not preceded by pilot studies to provide initial information on effectiveness and safety.								
Population	Study populations shall be representative of the intended post-market patient population, including aetiology and pathology. Include enough subjects, investigators, institutions to be representative.				Inclusion / exclusion criteria should be clearly defined				
	Disease-/device- specific inclusion criteria and criteria for institutions (case-mix, skills, training, facilities etc.) listed. Investigators and institutions should be representative for the intended patient and user populations.				-	As ISO 25539	-	Criteria should specify target population and accessible population.	
Interventions	No clear definition of the intervention demanded								
Comparator	Active control with comparable device or another active comparator. ISO 5840-2 OPC for established devices.				ISO 14155	ISO 14155	Existing control device, existing non-absorbable stents unless absorbable devices established as preferred mode of treatment	ISO 14155	
Outcome	Endpoints have to be prospectively specified								

Heart valves					Stents, grafts, patches				
Design recommendations	**ISO 5840-1 2021**	**ISO 5840-2 2021**	**ISO 5840-3 2021**	**ISO 5190 2018**	**ISO 7198 2016**	**ISO 12417-1 2021**	**ISO 17137 2021**	**ISO 25539-1 2017**	**ISO 25539-2 2020**
	Specify components of composite endpoint as secondary endpoint.				-		Specify components of composite endpoint as secondary endpoint		
	Annexes on endpoints: Normative: all endpoints 5840-1 annex L, adverse event classification 5840-2, -3, 5910 annex Q. Informative: all endpoints 5910 annex S, hazards, failure modes, evaluation methods 5190 annex G; imaging protocols 5840-2, -3 annex H, R.				No annexes on endpoints	Annex A: Informative: technical and clinical events	Informative: Description of device effects of failure and clinical effects of failure 25539-1, -2 annex B and B, C.		
Statistical Methods	Pre-specified statistical analysis and success criteria.				-				
	Justification of statistical methodology by the manufacturer				-				
	Sample size calculation: For pivotal trials standard of care and available safety and performance /effectiveness data on relevant therapies with similar intended use" should be considered. A minimum of 150 patients in each valve position for at least 1 year, at least 400 patient years required to assess late adverse events in pre-market setting for all heart valves. The calculation is based on an OPC (the AE rate currently accepted derived from empirical data). For (ISO 5840-2 800 patient years per single position valve due to lower AE rates are needed, but may be less for niche indications, rare diseases or less common patient populations.				Statistical justification of sample size calculation				
					-	Consider loss to follow-up in sample size calculation.		-	
					Enroll ≤ 50% of study population per site.	-		Enroll ≤ 35% of study population per site.	
	Intention-to-treat (ITT) analysis as base case additionally per-protocol (PP) analysis recommended, justification for those randomized, who did not receive an implant.				See ISO 25539-1, -2	Per-protocol analysis		All patients included in study should be reported, also those excluded from primary endpoint analysis.	

Heart valves					Stents, grafts, patches				
Design recommendations	**ISO 5840-1 2021**	**ISO 5840-2 2021**	**ISO 5840-3 2021**	**ISO 5190 2018**	**ISO 7198 2016**	**ISO 12417-1 2021**	**ISO 17137 2021**	**ISO 25539-1 2017**	**ISO 25539-2 2020**
Contextual factors, learning curve	CI shall be conducted in institutions with appropriate facilities, caseload, and case-mix and by investigators with appropriate experience, skills and training. Sites should be selected to accommodate a spread of clinical experience and exposure to the device while allowing a reasonable learning curve.				-				
Reporting	CIR comply with ISO 14155 In addition: Consideration of device-specific ISO annexes. ITT and PP analysis for RCT. If investigations have been conducted during follow-up, the percentage of patients receiving the investigation and how they were selected shall be stated. CI shall be registered in publicly available databases.				CI shall be carried out using ISO 14155		CI shall be carried out using ISO 14155 or equivalent publications.		
					In addition: list with specifications of clinical events in more detail and device specific.	Like ISO 7198 with device-specific adaptations.	In addition to ISO 14155 and 12417-1: rationale for follow-up intervals based on degradation profile of implant.	Like ISO 7198 with device-specific adaptations.	

CI: clinical investigation, CIP: clinical investigation plan, CIR: clinical investigation report, ITT: intention-to-treat, OPC: objective performance criterion, PP: per-protocol, RCT: randomized controlled trial.

[1]Number of study arms, type of control (randomized, literature, performance goal), blinding, prospective vs. retrospective.

4.3.10.3 Methods of development of ISO standards

There is no information in the general or device-specific ISO standards about the methods that have been used to develop recommendations. They should reflect the current state of science in the medical fields concerned and be based on systematic literature reviews.

Consortia of clinical experts, often with the participation of experts from regulatory agencies, also develop recommendations on trial design in their field, that are relevant for pivotal trials in the regulatory setting. Regarding trial designs for heart valve devices, for example, several consensus documents have been published by the 'Valve Academic Research Consortium' ([68], [69], [70], [71], [72]) and by other expert consortia which defined endpoints ([73], [74]). Only one of the heart valve ISO standards (ISO 5910) cited those consensus statements from these consortia that were available by their date of publication; it recommended in its Annex S on endpoints in clinical investigations for valve repair devices, following the most recent guidance from these consortia – but it is taking into account of recommendations from the relevant academic research consortia of clinical experts seems to be an exception.

The other three ISO standards do not list relevant consensus statements in their bibliographies, except for one on bleeding definitions [74]. Several guidance documents from expert consortia do exist In the field of cardiovascular implants, that relate to trial designs or endpoints ([75], [76], [77], [78]), but only one document was cited in one of the ISO standards (12417-1 on cardiovascular implants). It is an outdated version of guidance on standardized endpoints for coronary intervention trials [79], despite an updated document [75] having been published three years before the publication year of the ISO standard. The other ISO standards on cardiovascular implants ([57], [58], [60], [64]) do not mention or cite guidance documents from clinical expert consortia.

These observations suggest that consensus recommendations from expert consortia, although they strive to standardize the endpoints in studies, are not routinely considered by the task forces writing ISO standards for medical devices. It is unclear to what extent research reports are reviewed when ISO standards are drawn up.

A statement in ISO 5840-2 that the provided values of OPC criteria might be used without further justification seems questionable. Using OPC criteria involves a comparison with historical data, but when the practice of medicine is continually evolving, for example with more effective co-therapies influencing study endpoints, then OPC criteria also have to be continuously adapted.

Considering the important role that harmonized standards play in European legislation, and similarly in other jurisdictions, then methods should be described in detail and the standards should be based on scientific principles. At the least, this means that systematic literature reviews should be performed to inform the development of recommendations in device-specific ISO standards. Secondly there should be consultative procedures to allow qualified stakeholders to provide comments.

Although **methodological guidance on study design** is much less based on empirical evidence, ISO 14155 on good clinical practice could have benefitted from using or referencing methodological guidelines written by expert consensus groups in the field of evidence-based medicine. Examples are the recommendations for reporting clinical and observational studies that are available through the

EQUATOR network[12]. Some regulatory guidance documents such as MEDDEV 2.7/1 revision 4 [33] and the clinical evidence guidelines for medical devices from the TGA [14] do refer to these expert documents, and some leading scientific journals require authors to adhere to them. Using such tools might improve the quality of regulatory science, and using the same terminology might foster mutual understanding between stakeholders across the life cycle of medical devices.

4.3.10.4 Limitations of this review

Our review of ISO standards has several limitations.

Firstly, we could not undertake independent screening by two reviewers of the abstracts of ISO standards, because that would involve having to order full-text ISO publications for two reviewers whenever the abstract did not allow the first reader to determine if the ISO standard contains information relevant to the study design of CI. Each copy costs between 80 and 200 CHF. Instead, only one reviewer with access to the full texts of ISO standards decided whether relevant information is included. The second reviewer only ordered the full texts identified by the first reviewer and checked them for compliance with the inclusion criteria. Thus, some relevant device-specific ISO standards may have been missed.

Secondly, the sheet used to record extracts from the recommendations in ISO standards is a relatively rough grid of topics (see methods section). Sub-issues are introduced depending on the contents of the guidance documents. Due to limited resources, it was not possible to extract the text independently by two reviewers, although a check by a second reviewer would limit inaccuracies. We used pre-defined topics to limit arbitrariness of the selection of text to extract, but some subtopics in study design that are related to cross-cutting issues such as validity could be pertinent to more than one topic. The degree of detail recorded might vary across standards.

4.4 Recommendations for Clinical Investigations of Medical Devices from National Regulators, the European Union, and the International Medical Device Regulators Forum

Overall, we included 30 regulatory guidance documents.

Nineteen documents from national regulators come from six jurisdictions: Belgium [1], UK [3], Australia [2], Canada [1], Japan [1] and the USA [11]. We included seven guidance documents from the Medical Device Coordination Group, prepared for the legislation of the MDR ([34], [35], [36], [37], [38], [39], [40]), one guidance document from the European Commission under the legislation of the Medical Device Directives, which was declared still valid in most of its text parts by the MDCG [38], and three guidance documents from the International Medical Device Regulators Forum ([41], [42], [43]). The citations and exact references are listed in Table 40, Table 41, and

[12] https://www.equator-network.org/

	Uncertainty, sample size, pre-specification, validity	Subgroup analysis	Bayesian statistics	Adaptive design
FDA 2010 Bayes	-	-	2.2, 2.6-7, 4.5.-4.8, 5, 7.1	
FDA 2013 Design Pivotal Stud.	9.3-9.4, 10	For stratified subject selection see P in PICO	-	-
FDA 2014 Evaluation Sex-specific data	-	V.A (p14-16) V.B (p16-18) V.C (p18-19-20) See Appendix 1	-	-
FDA 2016 Adaptive Trial Designs	-		6.c	4., 9., 10.
FDA 2016 Collection Race and Ethnicity data	-	IV	-	-
FDA 2017 Evaluating and Reporting Age, Race, ethnicity data	-	V. A reference to guidance on sex-specific data See Appendix 1	-	-
FDA 2019b Uncertainty in Benefit-Risk Determination	p12 18,22 Significance level, uncertainty	-	-	-
FDA 2022 Health of Women	-	Priority 1 p13, 15	-	-
TGA 2022 Evidence requirements	SSC: 29, 32, 34 DS (81) (statistical power calculation), 86 MEDDEV ref 31/32, 33	-	-	-
MHRA 2021 CI. Statistical considerations	SSC:1.2 Uncertainty, pre-specification,2.1 MISS 2.2, 2.3	-	-	3.2
Canada 2013 Inclusion of women	-	1.5 p8, 2.2 p13f, p14, 2.6 p25	-	-
Japan 2017 Clinical Trial guidance	5. p13	-	-	-
MEDDEV 2.7/1 Rev. 4	A6 b, c, f	-	-	-
IMDRF 2019 CI	6.0 Statistical plan	-	-	-

Table 42, stratified by topics.

The recommendations are structured along eight topics:

- definition and classification of study types, levels of evidence;
- need for a clinical investigation;
- choice of study design for pivotal clinical investigations;
- investigation objective, general design issues, and PICO;
- statistical methods;

- contextual factors and learning curve;
- reporting of clinical investigations; and
- patient engagement in clinical investigations.

4.4.1 Definition and classification of study types, levels of evidence

Two documents ([14], [19]) provide classifications of study types. These are a guidance document from the FDA on "Design considerations for pivotal clinical investigations for medical devices", published in 2013, and the "Clinical evidence guidelines for medical devices. Version 3.1" published in June 2022 by the regulatory authority for medical devices in Australia, the Therapeutic Goods Administration (TGA) (14).

There is a description of **adaptive study designs** in the FDA document "Adaptive Designs for Medical Device Clinical Studies" that was published in 2016 [22]. In this guidance, different adaptive trial designs are described without a direct ranking of their levels of evidence, but with a discussion about the relative advantages or challenges of adaptive designs and about measures that can be taken to maintain scientific validity. All adaptive designs (i.e. studies with pre-planned interim analyses) are randomized studies. Methods for controlling Type I and Type II errors and for minimizing bias in the different types of adaptive study designs are described in the section on Statistical methods.

The third included guidance document was published by the MDCG in 2020. Its topic is the clinical **evidence needed for legacy devices** under the MDR, which are those devices that were CE-marked under the Medical Device Directives and that will continue to be placed on the market after the date of application of the MDR/IVDR.

The FDA document on **pivotal CI** [19] in its introduction, defines stages of the clinical development of medical devices and assigns different regulatory study types to each:

- In the **exploratory clinical stage** "the limitations and advantages of the medical device are evaluated. This stage includes first-in-human studies and feasibility studies".
- The **pivotal stage** is next. It "is used to develop the information necessary to evaluate the safety and effectiveness of the device for the identified intended use. It usually consists of one or more pivotal studies."
- The last stage is the "**post-market stage** which can include an additional study or studies for better understanding of device safety […] and long-term-effectiveness".

The FDA guidance "provides information on design issues related to pivotal clinical investigations and does not address the other stages in any detail" [19]. To determine the safety and effectiveness of therapeutic medical devices, clinical outcome studies are performed "in which subjects are assigned to an intervention and then studied at planned intervals using validated assessment tools to assess clinical outcome parameters or their validated surrogates" [19].

The FDA explains general principles of study design in chapter 6 of the guidance document, and it describes "advantages and disadvantages of some clinical outcome studies" in chapter 7.8. After stating that some study designs provide a higher level of evidence than others, and that the more bias

is minimized then the higher the level of evidence, it gives a description of the advantages and disadvantages of different studies in terms of minimizing bias that is close to providing a hierarchy of evidence. “Whenever a sponsor believes it is not appropriate or necessary for a clinical outcome study to be well-controlled, randomized and/or blinded, the sponsor should explain why the possible biases can be ignored” [19]. ‘Level of evidence’ is defined as “the collective level of confidence about the validity of estimates of benefits and harms for any given intervention” [11].

In Table 10 we summarize the definitions, advantages and disadvantages of study types as described in the FDA guidance document in its sections 7.8, 7.4 Table 1, other parts of section 7, and glossary. The criteria for controlling bias are randomization, which is the only measure that can control unknown confounders (7.2), blinding, and concurrent control groups. It is stated that a randomized, double-blinded, controlled parallel-group clinical study provides the highest level of evidence. It is recognized that this design might not be feasible for all medical devices because of difficulties with blinding.

The **randomized study in which the subject serves as their own control** is a special case of a randomized study with a concurrent control group; preconditions that have to be fulfilled include that the effect is evident only locally and that there is no carry-over effect. Its position within the hierarchy of levels of evidence is determined by whether or not the study is blinded to patients, treating physicians and those who evaluate outcomes. Without blinding, it would have the same lower level of evidence as an unblinded randomized study with a concurrent control group. This is not directly stated, but obvious from the criteria used to control bias.

A randomized study with a concurrent control group that is completely unblinded – with even the assessors not being blinded – requires a consultation with FDA staff to consider how concerns about bias could be addressed. A study where controls receive no intervention has a larger potential for bias than studies where controls receive an active treatment or a placebo intervention, because of the built-in bias coming from the expectation of no benefit in the control group compared to the intervention group (7.4, 7.5).

The next two study types in the table are non-randomized studies with concurrent controls; and single-group studies with comparison to baseline. Generally, these designs are not recommended, the first “since it is as labor intensive as a randomized study, but introduces more biases due to likely differences in the groups, sites, and investigators, including unmeasured but likely confounding differences”, and the second because any changes between baseline and follow-up may be caused by other factors than the treatment (such as placebo effect, or regression to the mean).

Single-group studies with results compared against historical controls or **objective performance criteria** (OPC) are not directly discouraged but their main problem is underscored, which is to achieve comparability between the groups. The single-group study with OPC is classified in chapter 7.6 as a non-comparative study and it is not considered a well-controlled study – a term used in the code of federal regulation – but it is explained that the FDA uses OPC derived from historical data from clinical studies and registries as pass/fail criteria for safety or effectiveness, and it is pointed out that there existed very few validated OPC at the time the guideline was published (2013):

> "An OPC is usually developed when device technology has sufficiently matured and can be based on publicly available information or on information pooled from all available studies on a particular kind of device. An OPC needs to be carefully constructed from a prior meta-analytic review of all relevant sources, and a subject-level meta-analysis is preferred. An OPC will tend to have greater validity if it is commissioned or adopted by a medical or scientific society or a standards organization or is described in an FDA guidance document. An OPC typically cannot be developed by a single company using only their data or based on their review of relevant scientific literature, nor is an OPC typically developed unilaterally by FDA. It is also important to note that an OPC can become obsolete over time as technology matures and improves."

When **performance goals** (PG) are used "generally, the device technology is not as well-developed or mature for use of a PG as for an OPC, and the data used to generate a PG is not considered as robust as that used to develop an OPC". Therefore a "PG provides a level of evidence that is inferior to the OPC". A PG might be considered for challenging patient populations or if there is no clinical equipoise for any control." Using a PG in a pivotal study needs discussion with the FDA.

Observational studies and registries are not considered in the weighing of advantages and disadvantages of study designs for pivotal studies. Comparing therapeutic effects in clinical databases is characterized as "fraught with bias", and confounding by indication due to the lack of randomization is offered as one explanation.

Table 10. Definition and classification of study designs for medical devices according to FDA 2013

Study design	Description	FDA advantages/ disadvantages
Randomized, double-blinded, controlled parallel group clinical study (active or placebo control)	A randomized study is a study in which participants are randomly (i.e. by chance) assigned to one of two or more interventions of a clinical study. Double-blinded indicates that the intervention assignment is not known to the subject or the study staff (including the investigator or any third-party evaluator(s)). Parallel group design means that each subject or sample is assigned only one of the possible treatments being compared. Because a different group of subjects (or samples) is assigned to each treatment, comparisons are made between subject groups. When considering an active control, an important consideration is whether to design the study to demonstrate superiority or non-inferiority.	This study design provides the highest level of assurance that the subject populations in the investigational and control groups are comparable and avoids systematic differences between groups with respect to known and unknown baseline variables that could affect both safety and effectiveness outcomes. However, there are devices for which this design is neither feasible nor practical. Deviation from this study design is especially problematic in situations where there is a possible placebo effect, or when subjective outcome measures are used as study endpoints. Choice of an appropriate active control is based on the current standard of care for the intended subject population. A placebo control is useful if there is thought to be a placebo effect. • It may be challenging to construct a placebo control that appears to function like the investigational device but delivers no therapy. • In some cases, it may be unethical to randomize subjects to a placebo that will provide no known effect.
Randomized, subject as own control, paired clinical study Two-group cross-over design study	In such a study design, the subject could be treated with both the investigational and control interventions at the same time (e.g. side of face). The assignment of intervention is randomized. Another type of such a study design is a two-group cross-over design study, where each subject receives the investigational and control	This study design is possible when the device effect is only evident locally. It is impossible to evaluate and differentiate systemic safety or effectiveness outcomes when using this study design. The advantage of this study design, when used appropriately, is that the effects of both interventions are measured in the same subject and the variability is smaller so a smaller sample size may be required.

Study design	Description	FDA advantages/ disadvantages
	interventions sequentially, with a randomly assigned order.	With the cross-over design one needs to assume that the effects of the first intervention will not carry over into the second intervention period. Otherwise, a "wash-out" period may have to be incorporated into the study.
Randomized, non-blinded study with concurrent control (Active, placebo or "no Intervention")	Incomplete blinding refers to instances where the subject, the investigator or the third-party evaluator is not blinded. When no one is blinded, the study is often referred to as an open-label study.	If the subject's assignment to an intervention is not blinded (masked), the behavior of the subject may be affected by knowledge of the intervention and consequently a bias can be introduced, particularly if a clinical measurement or endpoint is subjective. If the investigator or a third-party evaluator is not blinded (masked) to the intervention assignment, then investigator or evaluator bias can adversely affect the study by influencing the interpretation of clinical outcomes, the performance of surgical implantation of a device, and subsequent clinical decision-making (7.3). If study participants are not blinded, it is very difficult to assess the size of the resulting bias, and it can threaten the scientific validity of an otherwise solid study, even when a truly objective endpoint is used. In instances where blinding of any or all of the study participants (subjects, investigators, evaluators) is not possible, a detailed rationale and explanation of proposed means to address concerns related to bias should be provided to FDA. Choice of a "no intervention" control may present a challenge in recruiting subjects who might receive no intervention or keeping subjects enrolled who were randomized to the "no intervention" control group.

Study design	Description	FDA advantages/ disadvantages
		• Choice of a "no intervention" control has built-in bias because control group subjects expect to receive no benefit, whereas experimental group subjects expect to receive a benefit. • A "no intervention" control may sometimes be standard of care/best medical management which can provide evidence about any incremental benefit or risk, although the control could vary among the different study centers.
Non-randomized study with concurrent control (active or placebo or "no intervention")	In a non-randomized design with a concurrent active control, subjects and investigators are not blinded to the intervention assignment.	Consequently, this study design suffers from all the drawbacks of a randomized, non-blinded study with concurrent control design. In addition, because there is no randomization and each subject receives only one of the possible interventions, there is a very real possibility of a bias with unknown size due to intervention assignment. This design is generally not recommended since it is as labor intensive as a randomized study, but introduces more biases due to likely differences in the groups, sites, and investigators, including unmeasured, but likely confounding, differences. Even if there appears to be a balance between the two intervention groups for the study overall, there is likely no balance for each participating investigator such that there may be an investigator-by-device interaction, in which the advantage of the investigational device appears to differ by investigator.
Single-group study compared to baseline	Subject's outcomes at baseline compared to outcomes at endpoint evaluations.	Use of baseline outcomes as a comparison for outcome at the endpoint evaluations is inadequate for most therapeutic studies since subjects may improve for reasons unrelated to investigational device (e.g., regression to the mean, placebo effect). It is usually advisable to also have a randomized

Study design	Description	FDA advantages/ disadvantages
		group with an active or placebo control (or even a "no intervention" control). Such a randomized group in a blinded study will provide a much more stringent control and avoid placebo effect bias as well as temporal bias.
Single-group study with historical control or Information	Historical Control Group: A control group of subjects who were observed prior to the pivotal study. Data collected from this control group is used to compare the performance of the investigational device.	The obvious bias inherent in the use of a historical control is temporal bias, since the groups are not concurrent. The use of a comparator study separated in time can introduce severe and unknown selection bias. Concerns about comparability of groups and that practice of medicine has changed with resultant changes in the expected outcomes. Thus, the disadvantage of this design is that the subject outcomes in a historical control may not be discernible or applicable to the current population being targeted. It may be possible to use a propensity score model to assess the comparability of the two groups after the current study has been completed. There is no way to assess comparability until the subjects are enrolled and baseline collected and analyzed so this approach can be risky. This control presents a significant challenge in addressing the implications of missing data. Sensitivity and missing data analyses may potentially address some concerns associated with bias.
	Objective performance criterion (OPC): A numerical target value derived from historical data from clinical studies and/or registries and may be used by FDA for the comparison of safety or effectiveness endpoints.	If a historical control group is not available, the performance of a device may be evaluated through a comparison to a numerical target value, OPC or PG, pertaining to a safety or effectiveness endpoint. Such a study design shares all of the challenges and limitations of comparison to a historical control. In addition, there is no independent way to assess how

Study design	Description	FDA advantages/ disadvantages
	Performance goal (PG): A numerical value that is considered sufficient by FDA for use as a comparison of the pivotal study results with a safety endpoint, or an effectiveness endpoint.	comparable the current group may be with the historical groups from which the OPC or PG is derived, and it is impossible to quantify the bias. Since there is no control group involved in such studies, comparison to an OPC or PG cannot demonstrate either superiority or non-inferiority.

FDA: U.S. Food and Drug Administration, OPC: objective performance criterion, PG: performance goal.

In brief, the **hierarchy of evidence in study designs** that can be considered for a pre-market approval derived **from the FDA guidance** in descending order is:

- the randomized double- blinded parallel group study with active or placebo control,
- the randomized parallel group study with incomplete blinding; at least outcomes evaluators should be blinded, and active or placebo control groups are preferable to control groups without treatment,
- single-arm studies with historical controls with individual patient data, or
- single-arm studies with OPC or PG provide the lowest level of evidence.

Whereas it is clearly stated that studies with OPC provide higher evidence than PG, because the latter are usually based on less empirical evidence, there is not stated a direct hierarchical relation between historical controls and OPC, although historical controls with individual patient level data allow to calculate uncertainty measures and if covariates have been measured statistical adjustment methods can be used to increase the comparability of groups.

Appendix B of the FDA Guidance document[13] published in 2014 [20], contains a list with trial designs that the manufacturer should use to describe the level of evidence of the data necessary to support his/her application:

- Randomized, multi-arm, “blinded” study with concurrent sham (placebo) control
- Randomized, multi-arm, “blinded” study with concurrent (“active”) control
- Randomized, multi-arm, un“blinded” study with a control (control that is either active or consists of no treatment)
- Non-randomized study with concurrent (“active”) control
- Single-arm study with patient serving as own control (include designed single-arm crossover)
- Single-arm study with historical control (using patient-level data)
- Single-arm study with literature control (historical control)
- Single-arm study with objective performance criteria
- Single-arm study with performance goals
- *Registry*
- *Observational study*
- *Systematic review (meta-analysis with patient-level data)*
- *Meta-analysis based on summary information only*
- *Literature Summary*
- *Uncertain*

This list comprises additional study types that were not considered appropriate for a pivotal study (shown above in italics), and it lacks the randomized controlled cross-over design. Otherwise, it seems to represent the hierarchy of evidence already explained in the guidance document on design considerations from 2013 [19].

[13] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k).

The second document containing a hierarchy of evidence for study designs14 was published in June 2022 by the regulatory authority for medical devices in Australia, the Therapeutic Goods Administration (TGA) [14]. It includes guidance on clinical evidence requirements, sources of clinical data including clinical investigations, clinical evaluation, and requirements for specific device types. According to TGA "clinical investigations include feasibility studies, studies conducted for the purpose of gaining market approval, and those conducted following market approval".

The general section on clinical investigations does not provide a hierarchy of evidence, but the recommendations on trial design in the device-specific parts of the guidance state that "manufacturers who intend to conduct clinical trials should design trials to the highest practical NHMRC level of evidence". This refers to the "National Health and Medical Research Council (NHMRC) levels of evidence and grades for recommendations for developers of guidelines" [17] for classifying the level of evidence of studies. In the section on clinical evaluation (page 66), the concept and role of the NHMRC levels of evidence are described:

> "An important part of the clinical evaluation is determining the overall strength of the evidence presented. A widely accepted tool for ranking different types of study design is the National Health and Medical Research Council's (NHMRC) levels of evidence. The levels of evidence rank different study designs into a hierarchy according to their potential to adequately answer a particular research question […]. The hierarchy is based on the level of bias inherent in the study design. Using this hierarchy,
> - systematic reviews of randomized controlled trials represent the strongest level of evidence, followed by
> - individual randomized controlled trials,
> - pseudo randomized controlled trials,
> - non-randomized comparative trials, and
> - case series.
>
> The level (or sufficiency) of evidence ultimately affects the confidence that can be placed in the study results. Manufacturers should source the highest level of evidence available that demonstrates the safety and performance of the device for the intended purpose(s)" [14].

Table 11 lists levels of evidence of study types, except for level I which refers to systematic reviews. Within level II there is no distinction between randomized trials; it is expected that clinical evaluation is done using risk-of-bias tools to consider blinding and other criteria. The guidance lists appraisal tools available from the Cochrane Collaboration and other expert networks for evidence-based medicine (p 29f) [14]. The general section on clinical investigations does not comment on the level of evidence of CI. For trials of specific devices (total and partial joint prostheses, cardiovascular devices to promote patency or functional flow, implantable pulse generator systems), "the preferred design is a randomized controlled clinical trial and conditions should ideally represent clinical practice in Australia" (pages 66, 81, 114, 137).

[14] Clinical evidence guidelines for medical devices. Version 3.1.

Table 11. Description and classification of study designs for medical devices according to TGA 2022 referring to NHMRC [17]

Level of evidence / study design	Description from glossary
II Randomized controlled trial	The unit of experimentation (e.g. people, or a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared. Cross-over randomized controlled trials – where the people in the trial receive one intervention and then cross-over to receive the alternate intervention at a point in time – are considered to be the same level of evidence as a randomized controlled trial, although appraisal of these trials would need to be tailored to address the risk of bias specific to cross-over trials.
III-1 Pseudorandomized controlled trial	The unit of experimentation (e.g. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared
III-2 A comparative study with concurrent controls	
Non-randomized, experimental trial	The unit of experimentation (e.g. People, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared. This can include: (1) a controlled before-and-after study, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group. (2) an adjusted indirect comparison, where two randomized controlled trials compare different interventions to the same comparator i.e. the placebo or control condition. The outcomes from the two interventions are then compared indirectly.
Cohort study	Outcomes for groups of people observed to be exposed to an intervention, or the factor under study, are compared to outcomes for groups of people not exposed.
Case-control study	People with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/ non-exposure to the intervention or factor under study.
Interrupted time series with a control group	Trends in an outcome or disease are measured over multiple time points before and after the intervention is introduced to a group of people, and then compared to the outcomes at the same time points for a group of people that do not receive the intervention.

Level of evidence / study design	Description from glossary
III-3 A comparative study without concurrent controls	
Historical control study	Outcomes for a prospectively collected group of people exposed to the intervention are compared with either: (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (i.e. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention.
Two or more single arm study	The outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared. Unadjusted indirect comparisons: an unadjusted indirect comparison compares single arms from two or more interventions from two or more separate studies via the use of a common reference i.e. A versus B and B versus C allows a comparison of A versus C but there is no statistical adjustment for B. Such a simple indirect comparison is unlikely to be reliable (see Song et al 2000).
Interrupted time series without a parallel control group	Trends in an outcome or disease are measured over multiple time points before and after the intervention is introduced to a group of people and compared (as opposed to being compared to an external control group).
IV Case series with either post-test or pre-test/post-test outcomes	A single group of people exposed to the intervention. Post-test – only outcomes after the intervention are recorded in the series of people, so no comparisons can be made. Pre-test/post-test – measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared (also known as a 'before- and-after study').

In this section we did not include the EU guidance document MDCG-2020-6, on the clinical evidence needed for legacy devices [38], which gives a definition of 'level of clinical evidence' in the context of the MDR:

> "this terminology is used in the MDR with respect to requirements for demonstration of conformity with the relevant GSPR [General Safety and Performance Requirements] and overall benefit–risk. It is understood to encompass the amount and quality of evidence (i.e. its characterization by quality, quantity, completeness and statistical validity, etc.) required to demonstrate safety, performance and the benefit–risk conclusion of a medical device. It should not be confused with the term 'levels of evidence' (as used in evidence-based medicine) which

> is used to rank study designs and is only a part of the concept 'level of clinical evidence'." (page 5) [38]

The term "level of clinical evidence" corresponds to the term "body of evidence" in the terminology of evidence-based medicine for one or more end-points of a clinical evaluation by a systematic literature review. In the MDCG 2021-08 guidance 'Clinical investigation application/notification' [34], which provides a form to use when applying to a national regulatory authority for a clinical investigation, a description of the study design should be provided. Choices to be ticked are indicated.

The item "Design of the clinical investigation" mostly uses the categories from Annex I of ISO 14155: 2020 (see Table 1), which are:

- exploratory,
- confirmatory,
- observational,

summarizing all types of studies in humans, as well as the developmental stages pilot, pivotal, post-market stage.

However, the item "Design methodology" gives these options which are not from ISO 14155:

- case control,
- controlled,
- cross-sectional,
- double-blind,
- parallel,
- randomized,
- open, and
- other

ISO 14155 does not give a classification of design methodologies, but only examples in Annex A about the CIP.

The other guidance documents did not contain a classification of levels of evidence.

4.4.2 Need for a clinical investigation

We found nine guidance documents ([11], [14], [16], [20], [33], [38], [39], [41], [42]) that addressed either the question of when a CI is necessary ([11], [14], [16], [33], [38][39], [41]), or when equivalence exists ([14], [20], [33], [39], [42]), or both.

MEDDEV 2.7/1 on clinical evaluation [33], published by the European Commission in 2016 under the medical device directives, covers both topics. Clinical evaluation is defined as:

> "a methodologically sound ongoing procedure to collect, appraise and analyze clinical data pertaining to a medical device and to analyze whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's instructions for use." (6.1)

> "Clinical evaluation is conducted throughout the life cycle of a medical device, as an ongoing process. Usually, it is first performed during the development of a medical device in order to identify data that needs to be generated for market access. Clinical evaluation is mandatory for initial CE-marking, and it must be actively updated thereafter. […] it ensures that the evaluation of safety and performance of the device is based on sufficient clinical evidence throughout the lifetime that the medical device is on the market." (6.2)

It has to be determined during analysis of the existing clinical data whether additional clinical investigations are necessary, to generate any missing data that address the identified gaps "so that conclusions can be drawn with confidence in relation to conformity with the essential requirements:

- evaluation of the safety, performance and the benefit/risk profile;
- compatibility with a high level of protection of health and safety (that can be determined by considering current knowledge/ the state of the art, with reference to standards and available alternatives, risk minimization, patient needs and preferences);
- the acceptability of any undesirable side-effects;
- the risk of use error and
- the adequacy of the IFU [instructions for use] to the intended users, consistency between available information" (10.2c).

In Appendix A2 it is stated that "implants and high-risk devices, those based on technologies where there is little or no experience, and those that extend the intended purpose of an existing technology (i.e. a new clinical use) are most likely to require clinical investigation data" (A2).

The criteria to pay special attention to are:

- "new design features, including new materials
- new intended purposes, including new medical indications, new target populations (age, gender, etc.)
- new claims the manufacturer intends to use
- new types of users (e.g. lay persons)
- seriousness of direct and/or indirect risks
- contact with mucosal membranes or invasiveness
- increasing duration of use or numbers of re-applications
- incorporation of medicinal substances
- use of animal tissues (other than in contact with intact skin)
- issues raised when medical alternatives with lower risks or more extensive benefits to patients are available or have become newly available
- issues raised when new risks are recognized (including due to progress in medicine, science and technology) [and]
- whether the data of concern are amenable to evaluation through a clinical investigation

Data on the safety and performance of other devices and alternative therapies, including benchmark devices and equivalent devices, should be used to define the state of the art or identify hazards due to substances and technologies. This will allow the clinical data requirements to be established more precisely in relation to the intended purpose of a device. Precision in this analysis and the choice of

selected medical indications and target populations may reduce the amount of clinical data needed from additional clinical investigations" (A2).

The document **MDCG 2020-6 concerning legacy devices**[15] was published in 2020 [38]. It provides guidance on clinical data that are considered to provide sufficient clinical evidence for the conformity assessment of legacy devices under the MDR (3.0). Because of its additional requirements, evidence sufficient for market authorization under the MDD may be insufficient under the MDR because of changes in the state-of-the-art or newly identified risks. Other examples that are given include the need for additional clarity with respect to indications and contraindications by post-market surveillance, the new requirements for equivalence in the MDR which may reduce the data available for demonstration of conformity, and the more explicit definition of clinical data which may remove some previously used data sources. Therefore, post-market clinical follow-up studies may be necessary to generate new data.

> "Manufacturers should conduct a gap analysis with respect to the MDR requirements. If data gaps have been identified, there are different possibilities to bridge those gaps. While controlled clinical investigations might be the preferred method for collecting clinical data as part of the PMCF studies for some products, there are other possibilities to gather relevant clinical data in the field in order to close the clinical data gap. Other alternatives include, but are not limited to systematic reviews of clinical data published in the literature, evaluation of results from PMCF studies such as clinically relevant scientifically sound questionnaires or registries." (6.5e)

Appendix III provides a "**Suggested hierarchy of clinical evidence** for confirmation of conformity with relevant GSPRs [General Safety and Performance Requirements] under the MDR". It states that the suggested hierarchy is "ranked roughly in order from strongest to weakest (some variations may apply dependent on the device, GSPR for which evidence is required, and quality of individual data sources)".

The hierarchy comprises 12 levels of clinical evidence. It is stated that class III legacy devices and implantable legacy devices which are not well-established technologies (WET) should have sufficient data as a minimum at level four, whereas WET may be able to confirm conformity "via an evaluation of cumulative evidence from additional sources of levels five to twelve". There is no statement whether this minimum level would also apply to devices which do not have a former market authorization. A definition of a WET, which applies to all devices, and not only to legacy devices, is given in section 1.2: "The common features of the devices which are **well-established technologies** are that they all have:

- relatively simple, common and stable designs with little evolution;
- their generic device group has well-known safety and has not been associated with safety issues in the past;
- well-known clinical performance characteristics and their generic device group are standard of care devices where there is little evolution in indications and the state of the art; [and]

[15] Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC

- a long history on the market."

Any devices that meet all these criteria may be considered "well-established technologies".

To define '**the state of the art**', the MDCG guidance refers to the definition given by the IMDRF in "Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices":

> "Developed stage of current technical capability and/or accepted clinical practice in regard to products, processes and patient management, based on the relevant consolidated findings of science, technology and experience.
>
> Note: The state-of-the-art embodies what is currently and generally accepted as good practice in technology and medicine. The state-of-the-art does not necessarily imply the most technologically advanced solution. The state-of-the-art described here is sometimes referred to as the "generally acknowledged state-of the-art." [80]

Appendix III, giving details of the 12 levels of clinical evidence, is shown in Table 12. The level of clinical evidence for a device is the result of the appraisal and analysis of the available clinical data, in the clinical evaluation. According to MDR Article 2.48, **clinical data** means "information concerning safety or performance that is generated from the use of a device and is sourced from the following:

- clinical investigation(s) of the device concerned,
- clinical investigation(s) or other studies reported in the scientific literature, of a device for which equivalence to the device in question can be demonstrated,
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
- clinically relevant information coming from post-market surveillance, in particular post-market clinical follow-up".

For legacy devices, MDCG 2020-06 adds the category of :

- "other pre-market data, e.g. case reports on experience with the use of the device in question, such as compassionate or humanitarian exceptional use reports".

It is pointed out "that this kind of pre-market data may be more prone to bias, compared to those listed above" (6.2.1). It is specified that the following can be considered as post-market sources:

- "post-market surveillance clinical data, complaint and incident reports;
- post-market clinical follow-up studies, including post-market clinical investigations;
- independent clinical studies conducted using the device;
- device registries; [and]
- data retrieved from the literature" (6.2.2).

Table 12. Appendix III- Suggested hierarchy of clinical evidence for confirmation of conformity with relevant GSPRs under the MDR from MDCG-2020-6 (38)

Rank	Types of clinical data and evidence	Considerations / Comments
1	Results of high quality[1] clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc.	This may not feasible or necessary for certain well-established devices with broad indications (e.g Class IIb legacy sutures, which could be used in every conceivable patient population).
2	Results of high-quality clinical investigations with some gaps	Gaps must be justified / addressed with other evidence in line with an appropriate risk assessment, and clinical safety, performance, benefit and device claims. Assuming the gaps can be justified, there should be an appropriate PMCF plan to address residual risks. Otherwise, manufacturers shall narrow the intended purpose of the device until sufficient clinical data has also been generated.
3	Outcomes from high quality clinical data collection systems such as registries[2]	Is there sufficient evidence of the quality of the data collected by the registry[3, 4]? Are the devices adequately represented? Are the data appropriately stratified? Are the endpoints appropriate to the safety, performances and endpoints identified in the clinical evaluation plan?
4	Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptability justified[2]	Many literature sources fall into this category, due to limitations such as missing information, publication bias, time lag bias, etc. This applies equally to publications in the peer-reviewed scientific literature. However, for legacy devices where no safety or performance concerns have been identified, these sources can be sufficient for confirmation of conformity to the relevant GSPRs if appropriately appraised and the gaps are identified and handled. High quality surveys may also fall into this category.
Class III legacy devices and implantable legacy devices which are not well-established technologies should have sufficient clinical data as a minimum at level 4. Those devices which are well-established technologies may be able to confirm conformity with the relevant GSPRs via an		

Rank	Types of clinical data and evidence	Considerations / Comments
evaluation of cumulative evidence from additional sources as listed below. Reliance solely on complaints and vigilance is not sufficient.		
5	Equivalence data (reliable / quantifiable)	Equivalence must meet MDR criteria. It is normally expected that manufacturers should gather data on their own devices in the post-market phase, therefore reliance on equivalence should be duly justified, and linked to appropriate PMCF or proactive PMS.
6	Evaluation of state of the art, including evaluation of clinical data from similar devices* as defined in Section 1.2 of this document	This is not considered clinical data under the MDR, but for well-established technologies only can be considered supportive of confirmation of conformity to the relevant GSPRs. Data from similar devices may be also important to establish whether the device under evaluation and similar devices belong to the group of devices considered as “well established technologies” (WET). See section 1.2 in this document for the criteria for WET. Data from similar devices may be used, for example, to demonstrate ubiquity of design, lack of novelty, known safety and performance profile of a generic group of devices, etc.
7	Complaints and vigilance data; curated data	This falls within the definition of clinical data under MDR Article 2(48), but is not generally considered a high quality source of data due to limitations in reporting. It may be useful for identifying safety trends or performance issues. High volume data collected within a robust quality system may provide supportive evidence of device safety.
8	Proactive PMS data, such as that derived from surveys	This falls within the definition of clinical data under MDR Article 2[48], but is not generally considered a high quality source of data due limitations associated with sources of bias and quality of data collection. It may be useful for identifying safety concerns or performance issues.
9	Individual case reports on the subject device	This falls within the definition of clinical data under MDR Article 2 [48], but is not considered a high-

Rank	Types of clinical data and evidence	Considerations / Comments
		quality source of data due to limitations in generalising findings to a wider patient population, reporting bias, etc. It may provide supportive or illustrative information with respect to specific claims.
10	Compliance to non-clinical elements of common specifications considered relevant to device safety and performance	Common specifications which address clinical investigation or data requirements directly would rank higher in this hierarchy. Common specifications may address clinically relevant endpoints through non-clinical evidence such as mechanical testing for strength and endurance, biological safety, usability, etc.
11	Simulated use / animal / cadaveric testing involving healthcare professionals or other end users	This is not clinical data, but may be considered evidence of confirmation of conformity to relevant GSPRs, particularly in terms of usability, such as for accessories or instruments.
12	Pre-clinical and bench testing / compliance to standards[1]	Pre-clinical and bench testing may address clinically relevant endpoints through non-clinical evidence such as mechanical testing for strength and endurance, biological safety, usability, etc.

1 Refer to data appraisal considerations described in Section 6.3 of this guidance.
2 Please note that the Considerations / Comments listed in point 2 also apply to these studies.
3 http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-methodological-principles.pdf
4 http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf
5 This may be of interest in the case of application of Article 61(10).
* Similar devices: "devices belonging to the same generic device group. The MDR defines this as a set of devices having the same or similar intended purposes or a commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics" (section 1.2).
GSPR: General safety and performance requirements.

The IMDRF guidance on Clinical Investigation [41] from 2019 describes the process that should be used to clarify whether a clinical investigation is needed, primarily to support marketing authorization for a therapeutic device: "whether there are new questions of safety, clinical performance and/or effectiveness for the particular medical device and intended use". It states that:

> "generally, such questions are more likely to be generated for high risk and/or novel medical devices. For long established technologies, the clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of, for example, published literature, reports of clinical experience, post-market reports and adverse event data may, in principle, be adequate to establish the safety, clinical performance, and/or

> effectiveness of the medical device, provided that new risks have not been identified, and that the intended use(s)/purpose(s) has/have not changed" (5.0).

According to this document, steps in the process are:

- identifying the relevant "Essential Principles", i.e. specifics for safety and clinical performance, acceptability of benefit/risk) for the medical device and its intended use/purpose(s);
- performing risk management and analysis,
- conducting a clinical evaluation, which will demonstrate which clinical data are necessary. (5.0).

The **IMDRF guidance on Clinical Evaluation** from 2019 [42] does not provide additional information on how to identify the need for a clinical investigation.

The **"Clinical Evidence Guidelines for Medical Devices" from the TGA** states that the mix of clinical evidence sourced from clinical investigations, literature reviews, post-market data and "other clinical data (also known as real-world evidence)", […] "will be scrutinized more for higher risk devices and for those with greater novelty, with greater expectations around direct evidence and/or high-quality clinical investigation data" (page 20). The section on CI states that:

> "Clinical investigation data sourced directly from the device produces a higher level of confidence in its relevance and capacity to inform the safety and performance characteristics of the device and is the preferred option for fulfilling clinical evidence requirements" (page 21).

To decide if a CI is needed, the manufacturer should perform a gap analysis to assess whether already existing data are sufficient. For criteria to consider, the guidance refers to the EU MEDDEV 2.7/1 revision 4 on "Clinical evaluation", Appendix A2. Criteria requiring special attention are given on page 21 of the TGA document.

"Clinical Investigations of Medical Devices – Guidance for Manufacturers", published in 2021 by the Medicines & Healthcare Products Regulatory Agency (**MHRA**) in the UK, states that a clinical evaluation of the relevant scientific literature is needed to demonstrate if a device complies with the general safety and performance requirements. This could be "a critical evaluation of the results of all clinical investigations made" or a demonstration of equivalence by relevant scientific literature or both (page 4).

The guidance document lists circumstances when a CI should at least be considered, for the new approval of a device in the UK (page 10):

- "the device is an implantable or Class III medical device
- the introduction of a completely new concept of device into clinical practice where components, features and/or methods of action, are previously unknown
- where an existing device is modified in such a way that it contains a novel feature particularly if such a feature has an important physiological effect; or where the modification might significantly affect the clinical performance and/or safety of the device

- where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body or where the materials are to be used for a significantly longer time than previously, in which case compatibility and biological safety will need to be considered
- where a device, either UKCA/CE UKNI/CE marked or non-UKCA/CE UKNI/CE marked, is proposed for a new purpose or function
- where in vitro and/or animal testing of the device cannot mimic the clinical situation
- where there is a new manufacturer especially of a high-risk device."

The guidance also mentions as an alternative the possibility to use already existing clinical data generated for an equivalent device (pages 4, 10).

The **Ministry of Health, Labor and Welfare in Japan** released an English translation of "**Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices**" in 2017 [16]. Section 2 (pages 3-6) of the document provides guidance to determine when a new clinical investigation has to be performed for MD approval or whether already existing data are sufficient. A flow chart shows six steps to go through in the evaluation process:

- clarification of development concept,
- clinical positioning,
- comparison with approved medical devices,
- conceptual requirements,
- coverage of the data, [and]
- clinical trial plan.

The clinical positioning explains the use of the MD in clinical practice, which is relevant for understanding the "intended use" or the indication of the MD. Then the new device is compared to one or more approved MD, according to a given list of characteristics. Differences to approved devices should be identified. In the next step a risk analysis is demanded for the identified differences, and issues regarding efficacy and safety of the MD that need to be evaluated have to be identified and appropriate evaluation methods investigated. "Whether non-clinical studies will adequately cover the conceptual requirements or not will be a key point in determination of necessity of clinical trials."

The step "data coverage" consists of a clinical evaluation based on non-clinical data and clinical data from the literature. An unclear sentence indicates when a clinical trial should be conducted: "If there is an endpoint that has not been evaluated but is evaluated only in a clinical trial, a new clinical trial has to be conducted" (page 6). An Appendix called "exhibit 1" presents 11 cases where no CI was necessary. To be recognized in Japan, foreign studies have to use comparable clinical practice standards for studies, conforming with medical device GCP:

> "For realization of expedited access of the medical device to patients in Japan, it is particularly important to consider conducting a multinational clinical trial including Japanese, especially if the proposed medical device is completely new, and the clinical development has just started.

For this purpose, differences between foreign countries and Japan should be taken into account even at the development stage."

Further requirements are that intrinsic ethnic factors such as differences in body size or metabolism, and extrinsic factors such as differences in healthcare, should be considered. A detailed list of ethnic factors is given. If clinical safety and efficacy in Japan are evaluated on results from studies in foreign countries, and if the robustness of those studies to demonstrate any differences is not adequately justified, then clinical trials in Japan will be needed. In section 3.3.2, the document points out that device changes during development are typical. If a modified device is submitted for approval that differs from the device in the clinical investigations, then the differences should be clarified, and a justification is required that the results of the clinical investigation are still applicable. Otherwise, another clinical investigation has to be conducted (page 9).

An overview of the recommendations regarding the need for a clinical investigation, from these international regulatory authorities, is shown in Table 13.

Table 13. Recommendations regarding the need for an investigation in six guidance documents from four legislations and from the IMDRF

Criteria which may indicate a need for a clinical investigation	MHRA	TGA	PMDA	MEDDEV/ MDR*	IMDRF
The clinical evaluation will demonstrate which data are necessary	x[1]	x	x	x/x	x
New questions of safety					x
New questions of clinical performance or effectiveness					x
New questions regarding the intended use					x
Questions above more likely for high risk and/or novel devices		x			x
CI data may not be necessary for long established technology					x
Endpoint not yet evaluated that only can be evaluated in a CI			x		
New intended purposes, (indications, target populations)	x	x[2]		x	(x)[3]
New types of users		x[2]		x	
New claims of the manufacturer		x[2]		x	(x)[3]
When new risks are recognized		x[2]		x	(x)[3]
Alternatives with lower risks / more benefits (newly) available		x[2]		x	(x)[3]

Criteria which may indicate a need for a clinical investigation	MHRA	TGA	PMDA	MEDDEV/ MDR*	IMDRF
Data of concern are amenable through a CI		x[2]		x	
Seriousness of direct and /or indirect risks		x[2]		x	
An implantable or class III medical device	x			**MDR**	
New design features, including new materials		x[2]		x	
Completely new concept, components features and/or methods of action previously unknown	x				
Existing device with new features with possible physiological effect / effect on clin. performance or safety	x				
Incorporation of medicinal substances		x[2]		x	
Contact with mucosal membranes or invasiveness		x[2]		x	
Device with materials previously untested in humans, coming into contact with the human body	x				
Existing material applied to a new location in the human body	x				
Materials used for a significantly longer time than previously (case compatibility and biological safety considerations)	x				
Invitro and/or animal testing cannot mimic clinical situation	x		x		
Use of animal tissues (other than in contact with intact skin)		x[2]		x	
Increasing duration of use or numbers of re-applications		x[2]		x	
New manufacturer especially of high-risk device	x				

IMDRF: International Medical Device Regulators Forum, MEDDEV: Medical Device Directives, MDR: Medical Device Regulation, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), TGA: Department of Health, Therapeutic Goods Administration (Australia).

[1] MHRA document shows that clinical evaluation is the relevant process to determine the need of a clinical investigation: "Clinical investigations are also not required for implantable and class III devices that […] and [t]he clinical evaluation is based on sufficient clinical data and complies with relevant product specific common specification where available.

[2] TGA cites directly the MEDDEV criteria.

[3] considered similar to the three statements by IMDRF on safety, performance and intended use by the authors of the CORE-MD report. * See text regarding MDR.

Five guidance documents contain **recommendations on the equivalence of devices**, from regulators in the USA, Australia, the European Union and the IMDRF ([14], [20], [33], [39], [42]). These include an **FDA recommendation from 2014**[16] [20] and a section entitled "**Comparable devices including substantially equivalent devices"** on pages 47-55 of the Australian TGA [14]. The evaluation of equivalence of MD is not part of study design, so this is only a very short summary of the common features of the recommendations. Firstly, one or more comparable devices have to be identified; secondly, the intended use of the comparator device must be the same as of the investigational device; thirdly, technical, biological and clinical characteristics of the investigational device must be compared in a systematic way with the comparator device and the differences must be described; and fourthly, whether the identified differences would result in clinically significant difference in safety and performance has to be evaluated. If not, the devices are equivalent and usually a CI is not deemed necessary.

MEDDEV 2.7/1 rev. 4, in Annex A1, lists technical, biological and clinical characteristics that have to be considered for the demonstration of equivalence [33]. **MDCG guidance 2020-5** stated that the same criteria should be used under the MDR [39], while at the same time it clarified differences between these documents. In the MDR, equivalence is defined in Annex XIV, Part A, section 3. It is possible not to perform clinical investigations for high-risk devices by claiming equivalence, only if:

> "the device has been designed by modifications of a device already marketed by the same manufacturer and equivalence can be demonstrated according to the MDR" or for
>
> "an already marketed device not manufactured by him, in addition to the requirements in MDR Article 61(4), the manufacturer must have a contract in place that allows full access to the technical documentation on an ongoing basis"

The presumed equivalent device must have been certified under the MDR (4d pages 12/13).

The **guidance of the IMDRF on Clinical Evaluation** [42] specifies criteria for the "comparability" of devices in Annex A. This list contains criteria for intended use/purpose, and technical and biological characteristics, but not for clinical characteristics.

The guidance documents may define possible comparator devices or data requirements differently [14], which may determine if approval by equivalence without new CI can be used.

4.4.3 Choice of study design for pivotal clinical investigations

Seven documents recommend which study type is appropriate for pivotal clinical studies ([11], [12], [14], [16], [18], [19], [41]).

The **FDA** emphasizes that the choice of study design of a CI for a pre-market approval application "should consider both bias and variability" ([19], at page 19). Designs that introduce little or no bias are preferable to designs that do not control for bias:

[16] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)].

> "Whenever a sponsor believes it is not appropriate or necessary for a clinical outcome study to be well-controlled, randomized and/or blinded, the sponsor should explain why the possible biases can be ignored."(7.8) [19]

A second general consideration when evaluating a study design for level of evidence is "the sampling variability, which is controlled by the sample size of the study". This means that the study should have enough statistical power to investigate the presumed effect. The FDA guidance for the use of Bayesian statistics in medical device trials [18] also states that:

> "the basic tenets of good trial design are the same for both Bayesian and frequentist trials. It is recommended to follow the principles of good clinical trial design including use of randomization and blinding to minimize bias" (page 19f).

The type of analysis to be used (Bayesian or frequentist) should be chosen beforehand, because "switching to an analysis method that produces a more favorable outcome after observing the data is problematic" (page 20) [18].

The **TGA** "Clinical evidence guidelines for medical devices 3.1" [14] states in its generic part on clinical evaluation that "Manufacturers should source the highest level of evidence available that demonstrates the safety and performance of the device for the intended purpose(s)" (page 30). The evidence hierarchy used (see 4.4.1) ranks the RCT highest. In part 3 on requirements for specific device types, recommendations were made for the following therapeutic devices:

- total and partial joint prostheses,
- cardiovascular devices to promote patency or functional flow,
- implantable pulse generator or electrical nerve stimulation systems,
- heart valve replacements using a prosthetic valve, and
- supportive devices: meshes, patches and tissue adhesives.

The summary recommendations for all five types of devices repeat that the highest level of evidence should be sought for CI. The guidance for pulse generator systems also states "The preferred design is a randomized controlled clinical trial and conditions should ideally represent clinical practice in Australia". The recommendation on study type for implantable pulse generators was quite unspecific:

> "Regardless of design, clinical studies should provide unbiased results that allow an objective comparison of implantable pulse generators with respect to their safety and performance. To achieve this for new device applications based on direct clinical data the manufacturers should ensure that clinical trials are conducted according to internationally recognized standards for a given trial design, e.g. follow the ISO standard 14155".

The TGA recommendations for heart valve studies mainly refer to the ISO 5840 ([61], [62], [63]).

> The **MHRA** published two guidance documents on CI[117], in 2021 ([11], [12]). The first states that:

[17] "Clinical investigations of medical devices - guidance for manufacturers" and "Clinical investigations of medical devices - statistical considerations"

> "If control groups are necessary these should be randomized and prospective, except in exceptional and justifiable circumstances. Pivotal/confirmatory studies should have a control where clinically relevant and appropriate to do so. For all studies, lack of a control group should be justified. […] The decision as to whether a control group is necessary however, will depend on the aims of the investigation" (page 14).

The second guidance document elaborates on the reasons for the decision. In the section "Use and selection of controls" (pages 5 & 6) it is explained that:

> "Where the endpoints can be measured objectively, e.g. from radiological examination, the majority of clinical investigations of medical devices will not require a comparative group and a single arm study design will be sufficient to demonstrate the required objectives. […] In circumstances where the endpoints are subjective, e.g. improvement in pain, a control group will nearly always be necessary in order to validate the claims being made for the device in question. Similarly, if a clinical investigation is intended to evaluate an intervention with a device compared with an alternative/no intervention, then the design of the trial will need to include a control group. The safety and performance of the device is then evaluated through the comparison of differences in the diagnosis or outcome between the treated patients and the control group. A scientifically valid control population must be comparable to the study population in all important patient characteristic and prognostic factors".

Guidance from the **Japanese authority**[18] states in section 3 at page 7 on 'Basic concepts on clinical trial design and sample size' [16] that:

> "A confirmatory clinical trial is desirably conducted in a randomized controlled trial (RCT) design because this evaluation method relatively reduces bias and thus is considered to provide quality results. By contrast, evaluation in a single-arm study may be acceptable if accumulated clinical evidence allows an applicant to establish the target result to be achieved appropriately; factors that affect the clinical study results are identified to some extent; and consensus has been reached for endpoints and results to be evaluated in the clinical study. If historical data or registry data are used as control results, the use in question should be justified based on applicable patients, intended use, and clinical positioning".

It is not completely clear either in the text from the MHRA, or in the guidance document from the Japanese regulator, whether "where the endpoints can be measured objectively" or "the target results to be achieved" refer to the concept of objective performance criteria or objective performance goals, which could be used as a reference standard in single-arm studies.

The **IMDRF** guidance on clinical investigation states that "the design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address the residual risks, including aspects of clinical performance" [41]. Factors "that may influence the extent of data requirements" are listed, without further explanations:

- "type of medical device and/or regulatory classification;

[18] "Clinical trial guidance to facilitate the speedy and accurate approval and development of medical devices"

- novel technology/relevant previous experience;
- clinical application/indications;
- nature of exposure to the product (e.g. surface contact, implantation, ingestion)
- risks inherent in the use of the product (e.g. risk associated with the procedure)
- performance claims made in the medical device labeling (including instructions for use) and/or promotional materials
- component materials or substances
- disease process (including severity) and patient population being treated
- demographic, geographic and cultural considerations (e.g. age, ethnicity, gender)
- potential impact of device failure
- period of exposure to the medical device
- expected lifetime of the medical device
- availability of alternative treatments and current standard of care [and]
- ethical considerations"

Table 14 provides an overview of recommendations for the choice of study design, including general principles, randomization, blinding, and the choice of control groups. The table includes statements on control groups that are discussed in the next section, and on blinding that are reviewed in the section on validity in the chapter on statistical methods.

Table 14. Recommendations regarding choice of study type in seven guidance documents from four legislations and the IMDRF

Recommendation	FDA	MHRA	TGA	PMDA	IMDRF
General principles for pivotal studies					
Manufacturers should use highest level of evidence available to demonstrate safety and performance (Highest level = RCT)			X		
Study designs that introduce little or no bias are preferable to designs that do not control for bias. Explain why biases can be ignored when the study is not well-controlled, randomized and/or blinded. Deviation from this study design especially problematic in situations with possible placebo effect or with subjective study endpoints	X				
The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address the residual risks, including aspects of clinical performance.					X
Randomization					
Use randomization and blinding to minimize bias	X				
If control groups are necessary these should be randomized and prospective, except in exceptional and justifiable circumstances		X			
A confirmatory study should desirably be randomized and blinded				X	
Randomization procedure should always be organized centrally in multi-center trials		X			
Details of randomization schedule should not be contained in the main study protocol, but should be set out in an annex that could be withheld from the study site, and randomization schedule should be filed securely to ensure that blinding is secured		X			

Recommendation	FDA	MHRA	TGA	PMDA	IMDRF
Blinding					
In comparative studies, bias can be minimized if the subjects, investigators, and third-party evaluators are blinded to the intervention assignment.	X				
Randomized, non-blinded study with concurrent control (Active, placebo or "no intervention"). In instances where blinding is not possible a detailed rationale and explanation of proposed means to address concerns related to bias should be provided.	X				
Blinding should be used if this is practical / blinding in investigations of medical devices is often difficult or impossible		X			
Potential means when blinding study participants during the entire study is not possible					
Blinding of intervention assignment to staff and subjects until subjects have been screened and enrolled	X				
Blinding of subjects after the procedure to avoid differential drop-out	X				
More objective endpoints preferable to subject reporting outcomes	X	X			
Standardized script for clinical staff for follow-up questions to study participants	X				
Minimize bias by assuring that the outcome evaluator is blinded to the assignment of patients to the treatment groups		X			
Control groups					
Need of a control group					
Studies must be well-controlled (see under General Principles for pivotal studies)	X				

Recommendation	FDA	MHRA	TGA	PMDA	IMDRF
Pivotal/confirmatory studies should have a control where clinically relevant and appropriate to do so		X			
Decision as to whether a control group is necessary however, will depend on the aims of the investigation"		X			
For all studies (includes non-pivotal studies), lack of a control group should be justified		X			
If a clinical investigation is intended to evaluate an intervention with a device compared with an alternative/no intervention, then the design of the trial will need to include a control group		X			
Where the endpoints can be measured objectively, the majority of clinical investigation will not require a comparative group, a single arm study design will be sufficient		X			
When endpoints are subjective a control group is nearly always necessary		X			
Choice of control group					
The Code of Federal Regulations (21 CFR 860.7(f)(iv) in the US, cited in the FDA document, recognizes four types of comparisons: no treatments, placebo control, active treatment control, historical control	X				
No treatments. Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients; (CFR)	X				
Choice of no intervention has built-in bias because control group subjects expect to receive no benefit, whereas experimental group subjects expect to receive a benefit	X				
"No intervention" control may sometimes be standard of care/best medical management which can provide evidence about any incremental benefit or risk, although the control could vary among the different study centers.	X				

Recommendation	FDA	MHRA	TGA	PMDA	IMDRF
Placebo control. Where there may be a placebo effect with the use of a device, comparison of the results of use of the device with an ineffective device used under conditions designed to resemble the conditions of use under investigation as far as possible; (CFR)	X				
A placebo control is useful if there is thought to be a placebo effect. It may be challenging to construct a placebo control that appears to function like the investigational device. In some cases, it may be unethical.	X				
Active treatment control. Where an effective regimen of therapy may be used for comparison, e.g., the condition being treated is such that the use of a placebo or the withholding of treatment would be inappropriate or contrary to the interest of the patient; (CFR)	X				
Choice of an appropriate active control is based on the current standard of care for the intended subject population	X				
Historical control. In certain circumstances, such as those involving diseases with high and predictable mortality or signs and symptoms of predictable duration or severity, or in the case of prophylaxis where morbidity is predictable, the results of use of the device may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations who received no treatment or who followed an established effective regimen (therapeutic, diagnostic, prophylactic).(CFR)	X				
Randomized, subject as own control (paired or two-group cross-over design. Presumptions: Device effect is only evident locally, no carry-over effect, advantage is less variability and smaller sample size	X				
Non-randomized study with concurrent control (active or placebo or “no intervention”). This design is generally not recommended, since it is as labor intensive as a randomized study, but introduces more biases due to likely differences in the groups, sites, and investigators, including unmeasured, but likely confounding.	X				

Recommendation	FDA	MHRA	TGA	PMDA	IMDRF
Single-group study compared to baseline is inadequate for most therapeutic studies since subjects may improve for reasons unrelated to investigational device. It is usually advisable to also have a randomized group with an active or placebo control (or even a “no intervention” control	X				
Single-group study with historical control: Concerns about comparability of groups and that practice of medicine has changed with resultant changes in the expected outcomes. Thus, the disadvantage of this design is that the subject outcomes in a historical control may not be discernible or applicable to the current population being targeted. There is no way to assess comparability until the subjects are enrolled and baseline collected and analyzed so this approach can be risky.	X				
If a historical control group is not available, the performance of a device may be evaluated through a comparison to a numerical target value (objective performance criterion = OPC, performance goal = PG). Such a study design shares all of the challenges and limitations of comparison to a historical control. In addition, there is no independent way to assess how comparable the current group may be with the historical groups from which the OPC or PG is derived, and it is impossible to quantify the bias.	X				
An OPC is usually developed when device technology has sufficiently matured and can be based on publicly available information or on information pooled from all available studies on a particular kind of device.	X				
An OPC needs to be carefully constructed from a prior meta-analytic review of all relevant sources, and a subject-level meta-analysis is preferred.	X				
A PG refers to a numerical value (point estimate) that is considered sufficient by FDA for use as a comparison a for a safety or effectiveness endpoint.	X				
In some instances, a PG may be based on the upper (or lower) confidence limit of an effectiveness and/or safety endpoint	X				

Recommendation	FDA	MHRA	TGA	PMDA	IMDRF
An PG provides a level of evidence that is inferior to an OPC. Generally, the device technology is not as well-developed or mature for use of a PG as for an OPC, and the data used to generate a PG is not considered as robust as that used to develop an OPC.	X				
A PG might be considered for challenging patient populations or if there is no clinical equipoise for any control.	X				
An OPC or PG can become obsolete over time as technology matures and improves	X				
An OPC or PG will tend to have greater validity if it is commissioned or adopted by a medical or scientific society or a standards organization or is described in an FDA guidance document. An OPC or PG typically cannot be developed by a single company using only their data or based on their review of relevant scientific literature, nor is an OPC typically developed unilaterally by FDA	X				
Single-arm study acceptable if accumulated clinical evidence allows to establish the target result to be achieved, confounders are identified to some extent, consensus on endpoints.				X	
If historical data or registry data are used as control, this should be justified based on applicable patients, intended use, and clinical positioning				X	
A scientifically valid control population must be comparable to the study population in all important patient characteristic and prognostic factors		X			

CRF: Code of Federal Regulations, USA, FDA: U. S. Food and Drug Administration, IMDRF: International Medical Device Regulators Forum, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, OPC: objective performance criterion, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), RCT: randomized controlled trial.

4.4.4 General design issues, investigation objective, and PICO

Three documents give recommendations on **study objectives** of CI: two FDA guidance documents ([18], [19] and guidance from the MHRA regarding statistical considerations of CI [12]. The **FDA** guidance on design considerations for pivotal CI of MD states:

> "The study objectives provide the scientific rationale for why the study is being performed. The objectives should provide support for the intended use of the device, including any desired labeling claims. Claims can be supported statistically by formal hypothesis testing or by point estimates with corresponding confidence intervals. For pivotal studies designed to test a scientific hypothesis, the study objectives should include a statement of the null and alternative hypotheses that correspond to any desired claim" (6.1) [19].

The **MHRA** guidance states:

> "An effective and efficient design of a clinical investigation cannot be accomplished without a clear and concise objective. This must be formulated with great care and specificity. It is not adequate simply to state as an objective '[…] the safety and performance of a device […]'. The aims and objectives must be set out so as to evaluate accurately the particular use of the device in the target condition and with the appropriate population and must be properly established prior to any development of the clinical investigation plan/protocol. Such aims and objectives will provide the essential focus for the investigation and should also provide the basis for labelling indications once the device is placed on the market" (1.1) [12].

The FDA guidance on the use of Bayesian statistics in MD clinical trials does not directly define what a study objective should contain, but it states within a section on selecting relevant endpoints: "The objective of a clinical trial is to gather information from the patients in the trial to make inferences about these unknown endpoints or parameters" (4.2) [18].

Study population:

Eleven guidance documents make recommendations regarding the **study population** ([12], [14], [15], [16], [18], [19], [21], [24], [27], [28], [33]).

The **FDA** recommends that "Subjects selected for any clinical study should adequately reflect the target population for the device (i.e. the population for whom the device is intended) based on specific enrollment criteria and confirmatory laboratory or other testing" (6.4) [19]. To ensure that the study population is representative for the target population, eligibility criteria matching the key characteristics should be defined in the protocol, and should be adhered to during the conduct of the study:

> "FDA encourages sponsors to enroll subjects who would reflect the demographics of the affected population with regard to age, sex, race and ethnicity. Inadequate participation from some segments of the population can lead to insufficient information pertaining to device safety and effectiveness for important subpopulations. We recommend including a background discussion of prevalence, diagnosis and treatment patterns for the type of disease for which the

> device is intended, if appropriate. This discussion should include: sex- and race-specific prevalence; identification of proportions of women and minorities included in past trials for the target indication; and a discussion of plans to address any factors identified or suggested, which may explain the potential for under representation of women and minorities, if applicable. We recommend including a summary of this information in the protocol and investigator training materials. Consideration should be given to enrollment of investigational sites where recruitment of needed populations for the study can be more easily facilitated. In the description of the patient population […] and use of foreign data […], consideration of how each is applicable to the U.S. population and U.S. medical practice should be included in the study design." [19]

Further, FDA advises to consider patient-related factors (covariates) that may be related to outcomes (e. g. disease severity, sex, age, ethnicity) and be particularly important for the current study in the planning phase. If differences in performance in important subgroups are expected these subgroups should be adequately represented. Stratified subject selection, i.e. when subjects are selected separately from each subgroup, ensures adequate representation and may also improve the precision of the effect estimates in subgroups. In such studies "it is often wise to also consider stratified randomization in which randomization occurs separately in each of the pre-specified strata". An unstratified selection only according to pre-specified inclusion criteria may be appropriate if differences in performance by subgroups are not expected. (6.5) Also for site selection it should be taken care that subjects will be included:

> "who reflect the epidemiological distribution of the disease being treated with regard to variables such as sex, age, race, ethnicity, socio-economic status, and coexisting conditions" (6.6).

For a pivotal clinical trial the evaluation of safety and effectiveness typically needs to demonstrate consistent results in a larger multi-center study, which also contributes to a more representative sample of the target population.

> "Differences in outcomes among centers are very important in the evaluation of medical device study outcomes because they may reflect differences in subject selection, surgical technique, and clinician skills, as well as any learning curve, all of which could bias interpretation of study results."

In addition to patient characteristics depending on the device, diversity of sites regarding investigator or operator experience should also be representative for standard of care and practice of medicine. If additional training for novel devices is needed to facilitate safe use of the device, then sponsors should ensure that users in the study have the necessary training. In summary the FDA guidance document states:

> "A study to support a pre-market submission in the United States should be relevant to understanding the safety and effectiveness of the device when used in patients in the United States with regard to subject demographics, standard of care, and practice of medicine. This is

> important for studies conducted both in and outside of the United States. Studies that fail to meet these criteria may be inadequate to support approval of a device" (6.6).

The **FDA guidance document on Bayesian statistics** (18) recommends that investigators should describe their study population, in the study protocol (4.1), and collect patient characteristics that may influence the outcome, so that adjustments can be made for imbalances between study arms or to reduce variation to achieve a more powerful analysis (4.3). Further it is stated that the concept of the representative sample, which is needed to make inferences from the study population to the target population, can be expressed in the Bayesian analysis as the assumption of exchangeability of patients, i.e. patient outcomes do not depend on the order how patients are enrolled or analyzed (3.7).

The **MHRA** guidance on statistical considerations for CI emphasizes that:

> "the study population must be defined before the investigation by the development of strict, unambiguous inclusion and exclusion criteria. These criteria will characterize the study population and in this way help to define the intended use of the device. These criteria should also include an assessment of prognostic factors for the outcome variable(s) since one or more of these variables may influence the performance of the device, e.g. age, sex, stage of disease" (12).

For pivotal trials, "the patient populations should more closely mirror the intended treatment population" (1.3). In a controlled trial, imbalances of such confounding factors may bias the results (1.6). The selection of study sites is also considered as critical in planning a CI. The sites must be able to select enough eligible patients who are representative of the target population. The study centers must have appropriate facilities for processing patients according to the study protocol (1.7).

In **MEDDEV 2.7/1 revision 4** [33], in section 9.3.1a covering the evaluation of the validity of designs of pre- and post-market studies, it is recommended to consider whether inclusion and exclusion criteria, as well as stratification of patients (e.g. in respect to age, medical indication, severity of the condition, gender, other prognostic factors) are adequate, and whether the distribution of prognostic factors is comparable in case of multiple groups. What "adequate" exactly means is not stated. In section 9.3.1b it is stated that transferability of the results of a clinical investigation conducted outside the EU to the European population has to be considered.

In the clinical evidence guidelines for MD from the **TGA** [14] there is only an indirect reference to requirements for the study population. It is recommended to use a checklist from the IMDRF for the suitability of the data to be assessed. Under the criterion "appropriate patient group" the question is:

> "Were the data generated from a patient group that is representative of the intended treatment population (e.g. age, sex, etc.) and clinical conditions (i.e. disease, including state and severity)?" (page 31)

Further, in the device-specific parts as requirement for a CI of the MD under consideration, it is stated that "The eligible patient groups should be clearly defined with exclusion/inclusion criteria" (pages 81, 94, 128, 151).

The guidance of the **Japanese** regulatory authority mentions requirements for the study population only in the context of "handling of results from clinical trials in foreign countries", related to requests for expedited access (section 2.3.3)(16). A multinational clinical trial must include Japanese patients, and ethnic factors should be taken into account. It distinguishes between intrinsic factors such as differences in body size and morphology, and extrinsic factors such as the novelty of a procedure, differences in patterns of practice, qualifications of healthcare professionals, social and cultural background, and lifestyle (page 7).

Four guidance documents discuss requirements for study populations mainly to improve and ensure the **generation and analysis of data from all subgroups** which have been shown to be under-represented or insufficiently analyzed in MD studies, such as women, children, and special ethnicities ([15], [21], [24], [27]).

The three guidance documents by the FDA on these issues ([15], [21], [24], [27]) recommend identifying and considering in advance whether a variation in outcomes may exist depending on age, sex, gender, race, or ethnicity (III.D), and to consider this in an appropriate enrolment strategy. In section IV.B.1 of the guidance documents on sex-specific data [21] and on age-, race- and ethnicity-specific data [24], these recommendations are made for the promotion of under-represented groups:

- a wide variety of investigational sites should be included where recruitment of age, racial, and ethnic subgroups can be more easily facilitated;
- alternative communication strategies for study recruitment, informed consent and patient materials should be considered;
- revision of enrolment criteria or collecting data on different device use from registries or parallel cohorts should be considered;
- provisions to encourage diverse enrolment should be considered,
- investigation of reasons for under-enrolment should be considered,
- factors that generally increase recruitment and retention should be considered, and
- flexibility in follow-up visit scheduling with provision of child or elderly care should be considered.

More recommendations for the pre-specification and performance of subgroup-specific analyses from these documents are described in the section on statistical methods in this report. The first priority of the "Health of Women Strategic Plan" of the Center for Devices and Radiological Health of the FDA is "to improve the availability, analysis, and communication of sex- and gender-specific information for the safe and effective use of medical devices to improve and better understand performance of medical devices in women" (page 13)[27].

The guidance of **Health Canada** [15] on considerations for inclusion of women in clinical trials and for the analysis of sex differences, makes some recommendations concerning clinical investigations of pharmaceutical products. For example, irrespective of whether or not sex-specific differences are known from earlier study phases, phase III studies should pre-specify sex-specific analyses (paragraph

2.2). This is followed by a detailed section on the enrolment of women with special considerations, such as if there would be any indication for the prevention of pregnancies, and on special groups such as pregnant and breastfeeding women (paragraphs 2.3-2.5).

This advice is not directly relevant for our research question on recommendations for study design for high-risk medical devices, but it may be valuable when planning and implementing enrolment. The specific recommendations given for medical device studies are that:

> "clinical investigations should be designed to identify whether there are differences by sex that affect the safety and efficacy of the device, including the nature and extent of those differences" (section 2.6).
>
> "[…] known or foreseeable factors that may affect outcomes should be addressed in the study protocol including e.g., subject selection, stratified or randomized design or statistical analysis, and that ideally these studies should be powered for subgroup analysis, where appropriate, to be able to draw valid conclusions about sex differences in response to medical devices" (2.6).

The **FDA guidance on patient engagement** in trials [28] lists barriers to enrolment about which the advice of patient advisors should be sought.

Table 15. Recommendations regarding study population in eleven guidance documents from six legislations

Recommendation	FDA	MHRA	Health Canada	TGA	PMDA	EU MEDDEV
Representative for target population of device	X	X		X		
Applicability of foreign trials to national population, standard of care, diagnosis and treatment patterns	X				X	X
Eligibility criteria with key characteristics of target population	X					X [1]
Eligibility criteria strict, unambiguous / clearly defined		X		X		
Pre-specification of eligibility criteria	X	X		X		
Representative demographic subgroups (age, sex / gender, race, ethnicity) [2]	X			X		
Subgroup specific disease background information: prevalence, diagnosis, treatment patterns	X					

Recommendation	FDA	MHRA	Health Canada	TGA	PMDA	EU MEDDEV
Collect data before trial to generate hypotheses of subgroup[2] by treatment interaction	X		X			
Pre-specified analyses for sex-specific differences	X		X			
Stratified subgroup selection	X		X			
Stratified randomization	X		X			
Multi-center recruiting for representative study population	X	X				
Multi-center recruiting, diversity of sites regarding investigator skills	X					
Multi-center recruiting representative for standard of care, practice of medicine	X					
Sites enough eligible patients		X				
Sites with appropriate facilities to process patients according treatment protocol						
Data collection of covariates (prognostic factors)	X	X				
Data collection of covariates to explain subgroup-specific differences	X		X			
Use enrolment and retention strategies (selection of sites, communication, flexibility of follow-up visits, child and elderly care) that facilitate enrolment of underrepresented groups	X		X			
Engagement of patient experts to advise for enrolment	X					
Consider sample size for subgroup-specific analyses[2]	X		X			

EU: European Union, FDA: U. S. Food and Drug Administration, MEDDEV: Medical Device Directives, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), TGA: Department of Health, Therapeutic Goods Administration (Australia).

[1] Adequacy of inclusion and exclusion criteria, and comparable distribution of prognostic factors in study arms

[2] In the guidance document of Health Canada, the only subgroup addressed are women.

Intervention:

Six guidance documents ([10], [13], [19], [20], [33], [38]) contain recommendations on the intervention or the medical device. Four, from the European Union [33], Belgium [10], the USA [20] and the UK [13], provide detailed lists with items describing:

- the identification of the device,
- its technical and biological characteristics,
- its mechanism of action,
- its intended purpose,
- the indications for use,
- training needs,
- equivalence to a similar device,
- description of the equivalent device, [and]
- differences to the equivalent device, etc.

[See details in the A.10]

Recommendations on device descriptions have different purposes. MHRA guidance[19] and guidance from FAMHP[20] are part of the submission dossier for a clinical investigation of a medical device. In FDA guidance on pre-market submissions[21] the description of the device is required in the context of demonstrating equivalence to a similar device. In EU MEDDEV 2.7/1 Rev.4 from 2016 a description of the device is recommended in Appendix A3 in the context of clinical evaluation; appendix I of MDCG 2020-6 [38] lists all parts of MEDDEV 2.7/1. rev. 4 that are still valid under the MDR, including its Appendix A3. FDA guidance on pivotal studies[22] [19] recommends that the study protocol should include a "statement of the procedures (treatments and tests) that will be applied" (10).

Comparator:

Six documents ([12], [14], [16], [18], [19], [33]) give recommendations on comparators that are considered appropriate in CI of MD.

The most extensive guidance on **study controls** comes from the FDA guidance on pivotal clinical investigations [19]; in section 6.7, three comparative study designs are distinguished:

- the parallel group design, in which each subject receives only one of the possible interventions, and outcomes are compared between the different intervention groups;
- the paired design, in which each subject receives all treatment at the same time; and
- the cross-over design, in which each subject receives all interventions at different times but in a predetermined sequence.

[19] "Clinical investigations of medical devices – compiling a submission to MHRA"
[20] "Clinical Investigations. Guidance on Dossier Content"
[21] "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]"
[22] "Design considerations on pivotal clinical investigations for medical devices"

For the parallel group design, randomization of subjects to the intervention groups is recommended, to ensure comparable groups at baseline. The paired design has the advantage that smaller variability within subjects than between subjects, leads to higher precision of results, but it has the disadvantage that non-local adverse events can hardly be assigned to the intervention. The cross-over design is possible only if there is no carry-over effect to the next phase; the FDA recommends that the order of interventions should be randomized. Concurrent and non-concurrent controls are distinguished, in section 7.4, and the consequences regarding study validity are described. This description and evaluation, and that for non-comparative studies with objective performance criteria or performance goals (7.6), from which the order in levels of evidence was derived, have been already summarized in Table 10 above.

The **FDA guidance** on Bayesian statistics [18] distinguishes in section 4.4 between concurrent controls, self-controls, and historical controls. It states that self-controls and historical controls have more potential for bias because of possible problems with covariate adjustments, placebo effects, and regression to the mean. It mentions the distinction between active, inactive (no treatment), and placebo controls, and it underlines that Bayesian methods are especially useful with active controlled trials which seek to prove that a new device is non-inferior to an active control, or also that it is superior to no treatment or to a placebo control. The last comparison can be made with reference to previous studies of the active vs. an inactive control (sham or no treatment). It is stated that Bayesian methods can also be applied for combining information from historical controls, used as prior information for comparison with concurrent controls (4.4).

The guidance of **MHRA** on statistical considerations of CI [12] uses a similar classification of controls as the FDA: concurrent controls, self or cross-over controls, and historical controls. In addition, it defines 'passive concurrent controls' as "where the control group receives an alternative intervention, including no intervention, but is not under the direct care of the same clinical study investigator" (1.4). In terms of validity, it is stated:

> "Concurrent controls and, where applicable, self controls allow the largest degree of opportunity for comparability. The use of historical controls is the most difficult in assuring comparability with the study population since the practice of medicine in terms particularly of methods of diagnosis and criteria for treatment changes over time. There are often therefore differences in patient selections that may not be easily or adequately documented, and which lead to differences in outcome that are mistakenly attributed to the use of the new device."

When a control group is needed, has already been discussed in Section 4.4.3.

The guidance on trial design from the **Japanese authority** [16] states in its section on basic concepts for clinical trial design:

> "For a controlled study design, considerations should be given to ensuring clinically appropriate setting of the control group (active-device control, placebo, conservative treatment, surgical treatment, etc.) and use of an appropriate bias-minimizing method (randomized, blinded, etc.) according to the objective of the clinical trial."

The **TGA guidance** document [14] also provides little detail on the choice of control groups. Its section on appraisal of clinical data states that "Single arm studies (and other study designs) with no comparator arm are generally considered inadequate evidence" (page 28).

MEDDEV 2.7/1 Rev 4 [33][in section (d) of its Appendix A6[23]] refers to "lack of adequate controls". Situations are listed when bias or confounding are probable, in single-arm studies and in other studies that do not include appropriate controls:

- "when results are based on subjective endpoint assessments (e.g. pain assessment),
- when the endpoints or symptoms assessed are subject to natural fluctuations (e.g. regression to the mean when observing patients with chronic diseases and fluctuating symptoms, when natural improvement occurs, when the natural course of the disease in a patient is not clearly predictable),
- when effectiveness studies are conducted with subjects that are likely to take or are foreseen to receive effective co-interventions (including over-the-counter medication and other therapies), [and]
- when there may be other influencing factors (e.g. outcomes that are affected by variability of the patient population, of the disease, of user skills, of infrastructure available for planning/ intervention/aftercare, use of prophylactic medication, other factors)."

It is stated that in the described situations it is not adequate to draw conclusions using direct comparisons with external or historic data such as device registry data or data from published literature. "Different study designs may allow direct comparisons and conclusions to be drawn in these situations, such as randomized controlled design, cross-over design, or split-body design." (A6.d)

Outcomes:

Twelve guidance documents from five jurisdictions and the IMDRF ([11], [12], [14], [16], [18], [19], [25], [28], [33], [37], [38], [43]) give recommendations regarding **study endpoints**.

The **FDA** guidance on the design of pivotal clinical investigations provides detailed recommendations regarding study endpoints, which should be clinically meaningful and relevant to the stated study objectives and the desired intended use.

> "The pivotal study should be designed to demonstrate clinical benefit to the specified subject population rather than to simply demonstrate how the device functions" (7.1).
>
> "Whenever possible, the endpoint should be objective, be internally and externally valid, and determined with minimal bias."

More objective assessment methods should be preferred to subjective clinical assessments. "An independent adjudication committee may be warranted to adjudicate an endpoint, for example, when objective assessments do not exist and a subjective assessment is used, such as in the case of an

[23] "Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety."

interpretation of a radiograph." The chosen variables should be pre-specified as primary and secondary endpoints in the study protocol. The protocol should specify what endpoints are being measured, how, when and by whom (e.g. by a blinded assessor, adjudication committee) and how they will be analyzed statistically. Rules for adjudication of endpoints also should be pre-specified in the study protocol.

Subject-reported outcome instruments that are validated for the population and condition being treated, and consistent with the intended use, can be used when the outcome of interest is best measured from the subject's perspective. In the case of multinational trials, instruments should be interpretable and valid across cultures and languages. If composite endpoints, i.e. a pre-specified combination of more than one endpoint, are used, then the single components should also be analyzed separately to identify dominance of one of the components or lack of consistency in individual component results. The relative importance of each of multiple primary endpoints for study success should be described. Statistical approaches to deal with multiplicity issues and to control Type I error should be pre-specified in the protocol. Use of validated surrogate endpoints that directly correlate with clinical benefit may be appropriate. A primary endpoint should not be chosen if it is undefined or unobtainable for a substantial proportion of subjects. The time-points at which safety and effectiveness endpoints are evaluated "should take into account the time course for activity of the product, considering evidence from prior studies" (7.1). Changing study endpoints during the trial may seriously impact trial interpretation and data analysis (7.1).

The FDA guidance on Bayesian statistics [18] briefly summarizes desired characteristics of study endpoints:" Endpoints […] are the measures of safety and effectiveness used to support a certain claim. Ideally, endpoints are: clinically relevant, directly observable, related to the claims for the device, and important to the patient" (4.2). FDA guidance[24] from 2019 [25] describes which types of benefits and risks should be measured:

> "The type of benefit(s) – examples include but are not limited to the device's impact on clinical management, patient health, and patient satisfaction in the target population, such as significantly improving patient management and quality of life, reducing the probability of death, aiding improvement of patient function, reducing the probability of loss of function, and providing relief from symptoms. These endpoints denoting clinical benefit are usually measured directly, but in some cases may be demonstrated by use of validated surrogate endpoints." (IV A)

The role of patient-reported outcomes is mentioned:

> "Patient-Reported Outcomes (PROs) (e.g. scales or scores indicating patient's experience of pain or function) can be helpful for patients and health care practitioners when discussing treatment options and decisions, and may be used to demonstrate benefit for purposes of product approval" (IV.C).

[24] "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications"

Regarding harms, it is stated:

> "FDA assesses the extent of the probable risk(s)/harm(s) by taking into account the following factors individually and in the aggregate: Severity, types, number and rates of harmful events associated with the use of the device:
>
> - Device-related serious adverse events – those events that may have been or were attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.
> - Device-related non-serious adverse events – those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse event.
> - Procedure-related complications – harms to the patient that would not be included under serious or non-serious adverse events, and that do not directly result from use of the device. For example, anesthetic-related complications associated with the implantation of a device" (IV.B).

For a more detailed description the FDA uses adverse event codes for medical device reports, which is one of the tools provided for post-market surveillance[25]. The terminology is harmonized with the corresponding IMDRF terminology (see below) and updated on a continuous basis at least once yearly[26,27].

FDA guidance from 2022 on "**Patient Engagement** in the Design and Conduct of Medical Device Clinical Studies" [28] considers as important activities "Discussing with patient advisors their views on which potential endpoints are meaningful" and "Working with patient advisors to inform the concepts that should be captured by patient-reported outcome (PRO) measures in the clinical study to better reflect outcomes that are important to patients" (V.A). The guidance also emphasizes that involving patients should be considered

> "during the early planning phases of the clinical study so that their input can be incorporated while the study plan is being developed. Especially in innovative areas or new target patient populations, we encourage sponsors to confer with patient advisors when designing or planning the clinical study."

For more established areas it is suggested to seek input from patient advisors on draft study plans, to make the design more patient-centric (V.B)[28].

The **MHRA guidance on CI for manufacturers** [11] states on endpoints for CI:

[25] https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems
[26] https://www.fda.gov/medical-devices/mdr-adverse-event-codes/coding-resources-medical-device-reports
[27] https://www.fda.gov/medical-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities/mdr-adverse-event-codes

> "Care should be taken in choosing endpoints to ensure that this will support the stated aims and objectives of the clinical investigation under normal conditions of use. Methods of supporting the demonstration of these endpoints should, as far as possible, be objective, e.g. derived from the results of diagnostic or in vitro diagnostic tests, rather than be subjective, e.g. severity of symptoms."

Further reference is made to the **MHRA guidance on statistical considerations** [12]. This document emphasizes that selecting appropriate endpoints is central for the investigation objective and states that the endpoints:

> "should be subject to minimal bias and error and should be directly related to biological effects of the clinical conditions. […] The endpoints shall be determined and assessed using scientifically valid methodologies. The primary endpoint shall be appropriate to the device and clinically relevant" (1.1).

The pre-definition in the study protocol of primary and secondary outcome variables is demanded. Generally, the primary outcome variable should provide the "most relevant and convincing evidence directly related to the primary objective", and only one primary outcome variable should be specified and used for the sample size estimation. But the selection of other primary variables is acknowledged to be desirable if a range of effects has to be covered. Secondary outcome variables are characterized to support further measurements related to either the primary objective or to a secondary objective if one had been determined (1.6).

The guidance from **Japanese authorities** contains a short section on requirements for the primary endpoint:

> "The primary endpoint shall be established to be as objective in clinical settings as possible in consideration of the intended use of the medical device and clinical significance. If a surrogate endpoint is used as an endpoint, use of the surrogate endpoint in evaluation shall be justified, including a relationship to the true endpoint."

The **MDCG guidance 2021-06** on "Questions & Answers regarding clinical investigation" [35] first provides the definition of a clinical investigation according to the MDR, which is: "any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device" (MDR article 2(45)). Subsequently the document summarizes the definition of the terms "performance", "clinical performance", and "clinical benefit" according to the MDR as:

> "the performance of a device is its ability to achieve its intended purpose as stated by the manufacturer. By extension, the clinical performance of a medical device is the ability of the device to achieve its intended purpose, thereby leading to a clinical benefit when used as intended. Clinical benefit means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health".

Further explanations of what this may mean for the clinical endpoints of clinical investigations are not given.

The **MEDDEV** guidance makes recommendations on outcomes, in Annex A7 "Analysis of the clinical data – compliance to specific Essential Requirements". Outcomes relevant to benefits and risks are considered in sections A7.2b-d.

Regarding the evaluation of the device's benefits, it is stated that:

> "positive impacts of a device on the health of an individual should be meaningful (relevant for the patient) and measurable. The nature, extent, probability and duration of benefits should be considered."

Relevant benefits that are mentioned are:

- the "positive impact clinical outcome (such as reduced probability of adverse outcomes, e.g. mortality, morbidity; or improvement of impaired body function",
- the patient's quality of life, [and]
- public health impact (A7.2b).

To quantify benefits, specified endpoints and how to measure them have to be defined. The clinical relevance of changes in endpoints has to be discussed and justified, and ideally, they should be directly clinically relevant. The probability of experiencing one or more benefits in different subgroups is considered another important aspect in evaluating benefits, as well as the duration of the effects (A7.2c).

To evaluate risks, the "nature, severity, number and rates of harmful events associated with the device" should be considered, as well as their probability and the duration of harmful events (7.2d). The same classification of adverse events and nearly identical wording is used as in the **FDA guidance** on factors to consider when making benefit-risk determinations [25] (see above); but in section 4 the definition of a serious adverse event includes in addition in-patient or prolonged hospitalization, and foetal distress, death or a congenital abnormality or birth defect. The full definition of a serious adverse event is given as an:

> "Adverse event that
>
> a) led to death,
> b) led to serious deterioration in the health of the subject, that either resulted in
>
> 1) a life-threatening illness or injury, or
>
> 2) a permanent impairment of a body structure or a body function, or
>
> 3) in-patient or prolonged hospitalization, or
>
> 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
>
> c) led to foetal distress, foetal death or a congenital abnormality or birth defect.
>
> NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event" (4).

This definition is taken from ISO 14155, which was cited [33]. Appendix A6 lists "improper collection of mortality and serious adverse event data" as a possible reason for lack of validity of a study if loss to follow-up is an issue. "In mortality studies (and other studies addressing serious outcomes) procedures for investigating serious patient outcomes, numbers of subjects lost to follow-up, reasons why subjects leave the study, and the results of sensitivity analysis should be fully disclosed in reports and publications." (A6e)

The **MDCG guidance 2020-6** [38] on evidence needs for legacy devices, in its section on clinical evaluation (6.1c, 6.5), refers to MEDDEV 2.7./1 Appendix A7.2b and c regarding endpoints for benefit and risks. MDCG 2020-6 confirmed in its Appendix I that this part of MEDDEV 2.7/1. is still considered as relevant guidance under the MDR. However, MDR article 2(58) contains an additional definition of an SAE as "a serious deterioration in the health of the subject, that resulted in a chronic disease". Later MDCG guidance on safety reporting in clinical investigations under the MDR **[MDCG 2020-10/1** (37)] provided the modified definition of SAE from MDR Article 2(58).

According to MDR article 73, the following events have to be reported without delay to all member states in which a clinical investigation is being conducted:

> "a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
>
> b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
>
> c) any new findings in relation to any event referred to in points a) and b)"

This also requires a determination of the causal relationship of the event(s) with the device or device-related procedure:

> In the clinical investigation "the relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered." [9]

It is stated that for harmonization of reports of SAE, four levels of causality are applied:

1. Not related,
2. Possible,
3. Probable, [or]
4. Causal relationship.

For each category, investigators and sponsors have to use the detailed definitions that are given, and consider these criteria:

- presence of temporal relationship with the use of the device or procedure,
- known response patterns to the medical device,
- impact of discontinuation and reintroduction of device application,
- body-site or organ to which the device was applied to,
- attribution to other causes, [and/or]
- event due to error in use.

For cases in which the relationship cannot be assessed or for which no information is available, or when a relationship may be weak but cannot be completely ruled out, then it has to be classified as "possible". The relationship should be classified as "probable" when it "seems relevant and/or the event cannot be reasonably explained by another cause" [9].

Further SAE related to the device or to the procedure will have to be distinguished, but SAE can also be related to both. Whether complications from concomitant treatment are considered as related, depends on whether or not they have been imposed by the CIP; If they have not, or if they result from routine diagnostic or patient management procedures that would have been applied regardless of the CIP, then the complications are considered as "not related".

Sponsors and investigators have to "make a maximum effort to define and categorize the event" and avoid situations of insufficient or contradictory data, and

> "particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand" (9).

The **MDCG guidance 2021-6** [35] on "Questions & Answers regarding clinical investigation" refers to **MDCG 2020-10/1**, concerning the reporting of safety.

The **TGA guidance** [14] provides recommendations regarding outcomes, not in its section on clinical investigations, but in the section on clinical evaluation and in part 3 of the document for each single device. The general statements on outcomes for studies are as follows:

> "Clinical safety and performance should generally be expressed in terms of person-centered outcomes, such as mortality, morbidity, adverse events, and patient reported outcome measures (PROMs). Where study findings are expressed in terms of markers or intermediate measures of safety and performance, a clinically reasoned argument should be provided linking the study findings with patient centered outcomes."

The IMDRF published a guidance document "IMDRF terminologies for categorized Adverse Event Reporting (AER): terms, terminology structure and codes" in 2020 [43]. The goal was to develop a globally harmonized terminology and associated codes for adverse events in the pre- and post-market setting.

> "The adverse event terminology outlined here consists of four main sets of specific terminologies […] and is intended to facilitate the reporting of: observations at the level of the medical device, its components including accessories, observations (typically adverse effects on health) at the level of subjects, i.e. patients, users or other persons, investigations into possible causes of the event as well as causal links between use of the device (independent of whether malfunctioning or not) and adverse health effects." (4.2)

The coding assigns alphanumeric codes to the predefined terms to further reduce ambiguity. "The complete adverse event terminology is comprised of seven annexes within four distinct sets of terminologies and their associated alphanumeric codes (Figure 2* and Table 1†). It is expected that terms will be used from each annex to fully capture the adverse event" (4.4).

Figure 1 below shows Figure 2* of the IMDRF guidance document.

Table 16 shows Table 1 of the IMDRF guidance document.

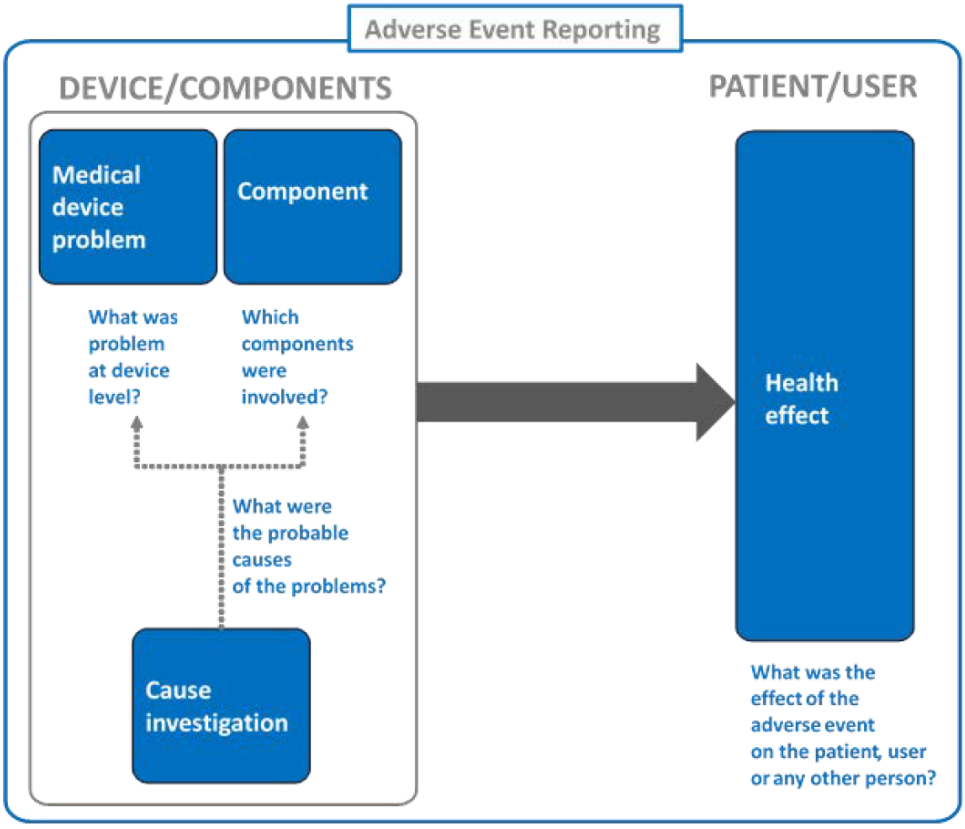

Figure 2: *The Adverse Event Reporting terminology is composed of four sets of terminologies: (1) Medical device problem terminology, (2) components terminology, (3) cause investigation terminology and (4) Health Effects terminology. Note that for an effective monitoring of adverse events, means of effectively identifying devices as well as the category they belong to (e.g. GMDN) are important.*

Figure 1. Overview of how to categorize adverse events [43] (Source: Figure 2 (with its legend) from the IMDRF guidance)

Table 16. Four sets of terminology for reporting adverse events, from Table 1 of IMDRF guidance [43]

No.	Name of terminology	Description	Annex	Coding system
1	Medical device problem	Terms/codes for describing problems (malfunction, deterioration of function, failure) of medical devices that have occurred in pre- or post-market contexts (e.g. clinical studies, clinical evaluation or post-market surveillance)	A	A|00[00][00]
2	Cause investigation - Type of Investigation	Terms/codes for describing the type of investigation of the device involved in the reported event.	B	B|00
	Cause investigation - Investigation Findings	Terms/codes for describing the findings of the device involved in the reported event.	C	C|00[00][00]
	Cause investigation - Investigation Conclusion	Terms/codes for describing the conclusion of the device involved in the reported event.	D	D|00[00]
3	Health Effects - Clinical Signs, Symptoms and Conditions	Terms/codes for describing the clinical signs, symptoms and conditions of the affected person appearing as a result of the medical device adverse event/incident.	E	E|00[00][00]
	Health Effects - Health Impact	Terms/codes for describing the consequences of the medical device adverse event/incident on the person affected.	F	F|00[00][00]
4	Component	Terms/codes for describing the parts and components which were involved in, or affected by, the medical device adverse event/incident.	G	G|00[000][00]

The terminology set on health effects corresponds with the level of the adverse event terminology used in the EU guidance documents and in the FDA document relevant for pre-market clinical investigations (see Table 17). The adverse event terminology is continuously updated. Therefore, a detailed maintenance plan was developed[28].

[28] https://www.imdrf.org/documents/maintenance-imdrf-ae-terminologies

Table 17. Items for annex F: Health impact from Table 3 of IMDRF guidance (43)

Change in Therapeutic Response	Recognised Device or Procedural Complication
Death	Reduction in Life Expectancy
Brain Death	Sedation
Delay to Diagnosis	Rehabilitation
Delay to Treatment / Therapy	Surgical Intervention
Disruption of Subsequent Medical Procedure	Serious Public Health Threat
Exacerbation of Existing Condition	Unexpected Deterioration
Hospitalization or Prolonged Hospitalization	Unexpected Diagnostic Intervention
Fetal Harm	Unexpected Medical Intervention
Inadequate / Inappropriate Treatment or Diagnostic Exposure	Insufficient Information
Minor Injury / Illness / Impairment	Unanticipated Adverse Device Effect
Serious Injury / Illness / Impairment	No Health Consequences or Impact
Misdiagnosis / Misclassification	No Patient Involvement
Prolonged Episode of Care	Appropriate Term / Code Not Available

Table 18 and Table 19 present an overview of recommendations on endpoints in the guidance documents of the different jurisdictions.

Table 18. Recommendations regarding endpoints in eight guidance documents from five legislations

Recommendation	FDA	MHRA	TGA	PMDA	EU [1]
Endpoints should be relevant for stated study objectives, intended use and support a certain claim	X	X			
Endpoints should be clinically meaningful, important for the patient	X	X	X		X
Clinical relevance of magnitude of benefits should be justified					X
Use of validated surrogate endpoints that directly correlate with clinical benefit might be appropriate	X		X		X
Use of a validated surrogate endpoint must be justified			X	X	
Endpoints should be pre-specified as primary and secondary endpoints in study protocol	X	X			
The primary endpoint should be most relevant and most convincing evidence directly related to the primary objective		X			
Only one primary endpoint, which is used for sample size calculation, but further primary variables possible		X			
Primary endpoint should not be unobtainable for a substantial proportion of subjects	X				

Recommendation	FDA	MHRA	TGA	PMDA	EU [1]
Secondary endpoints either support further measurements related to the primary objective or to a secondary objective		X			
Measurement methods of endpoints should be prespecified in study protocol	X				
Endpoints should be objective, objective assessment methods preferred to subjective ones	X	X			
Endpoints should be related to the biological effects of the clinical condition		X			
Endpoints should be determined and assessed using scientifically valid methodologies		X			
Endpoints should be subject to minimal bias and error	X	X			
Endpoints should be directly observable	X				
Subjective-reported endpoints (PROs) validated for population and condition, if outcome is best measured from subject's perspective	X				
PROs in multinational trials should be valid across cultures and languages	X				
Independent adjudication committee when objective methods do not exist	X				
If composite endpoints are used, the single components should also be analyzed separately	X				
Relative importance of single components of composite endpoints for study success should be described	X				
Approach for multiplicity issues from testing endpoints should be prespecified in study protocol	X				

FDA: U. S. Food and Drug Administration, MEDDEV: Medical Device Directives, MDCG: Medical Device Coordination Group, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), PRO: patient reported outcome. TGA: Department of Health, Therapeutic Goods Administration (Australia),

[1] From MEDDEV and MDCG documents

Table 19. Recommendations on types of outcomes from FDA, TGA, EU

Type of outcomes recommended to be used	FDA	TGA	EU [1]
Benefits (examples)			
Reducing probability of death	X	X	X
Improvement of patient health / morbidity	X	X	X
Quality of life / patient reported outcomes	X	X	X
Improvement of patient function	X		X
Reducing probability of loss of function	X		
Impact on clinical management	X		X
Public health impact			X
Risks			
Adverse events		X	
Device-related serious adverse events	X		X
Device-related non-serious adverse events	X		X
Procedure-related complications	X		X
Categorization of causal relationship			X[2]

FDA: U. S. Food and Drug Administration, MEDDEV: Medical Device Directives, MDCG: Medical Device Coordination Group, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), PRO: patient reported outcome. TGA: Department of Health, Therapeutic Goods Administration (Australia).
[1] From MEDDEV and MDCG documents, [2] from MDCG documents only

Regarding **device-specific recommendations**, five specific classes of therapeutic devices are covered in part 3 of the **TGA guidance** document:

- Joint prostheses,
- cardiovascular devices to promote patency or functional flow,
- implantable pulse generator systems including active implantable cardiac devices and electrical nerve stimulation devices,
- heart valve replacements using a prosthetic valve,
- supportive devices including meshes, patches and tissue adhesives, and
- software as medical device.

In this report we only present the recommendations on medical devices that meet our inclusion criteria. Thus, we do not present recommendations on supportive devices, electrical nerve stimulation devices and software.

The requirements for, or definitions of, outcomes for each of the devices are described in the section of the TGA document entitled “Measuring clinical success”. Outcomes for clinical performance and safety are listed for each device type, having been identified and compiled by TGA through analysis of relevant systematic reviews, HTA reports and trials. The tables listing outcomes are characterized as indicative.

For heart valves and coronary stents, recommendations for the use of standardized endpoint definitions were also available from academic research consortia. In the case of heart valves, it is explicitly recommended as a minimum to use the outcomes suggested by the Valve Academic Research Consortium [72]. For coronary stents, it is indicated that the European Commission has adopted the ARC recommendations [79] into their device-specific guideline (Appendix 1 from 2008 of MEDDEV 2.7/1) and it is advised to use the same standardized endpoint definitions. In addition, for heart valves the TGA adopted the recommendations from ISO 5840, that objective performance criteria should be used for the evaluation of prosthetic heart valves, and that the minimum of a sample size should comprise 400 valve-years of follow-up for each valve type in a clinical investigation.

The use of “performance values” was also considered for some of the other devices. For joint prostheses, the performance values for cumulative percentage revision (CPR) rates have to be taken from the Australian Orthopedic Association National Joint Replacement Registry annual reports. It should be demonstrated as a minimum that CPRs for the device under investigation are equal to or better than published CPRs for joint prostheses of the same class as defined by the Australian registry or another international joint registry, within the first two years (page 84).

For three other devices (carotid stents, peripheral stents, implants for patent ductus arteriosus (PDA) repair) it was stated that performance values cannot be provided because of the heterogeneity of patient characteristics, devices, operator experience, or primary endpoints. Instead, the manufacturer is required to justify its selection of clinical outcomes and values that define success.

For joint prostheses, the use of surrogate outcomes for predicting long-term device failure was encouraged, but with requirements for a justification of the selection and for the use of validated measurement tools where possible. Further, the TGA guidance presents the values for minimally clinically important differences (MCID) for different functional and quality of life scores used to evaluate the clinical performance of joint prostheses identified in the literature review. MCIDs and the success margin can be used to provide a minimum effect size and to calculate the sample size of the clinical investigation (page 85).

For joint prostheses, cardiovascular implants and heart valves, it is stated that “analysis of clinical events should be blinded and independently adjudicated wherever possible” (pages 81, 94 , 128). For more details on recommendations on outcomes for specific devices see Table 20 and

Table 21.

Table 20. Recommendations from the TGA guidance on outcome measures for clinical investigations for specific medical devices. Part 1.

	Joint prostheses	Active implantable cardiac devices (AICD)	Heart valves
Safety outcome	Primary safety outcome is revision reported as cumulative percent revision (CPR) based on the time to first revision p83-84 Table 7 p85-86	12 peri-procedure events and longer-term safety outcomes were derived from systematic reviews of AICDs.	Safety and performance outcomes not separated It is recommended to report the following variables as a minimum: 14 outcomes to report at 30 days, 11 outcomes after 30 days, 8 outcomes after 1 year. "Manufacturers should report early (within 30 days post implantation) and late valve outcomes (after 30 days post implantation) with a follow-up of one year or more (two years if seeking reimbursement) and a minimum of 400 valve years of follow-up for each valve type." Outcomes were taken from the consensus report of VARC from 2012, for appropriate definitions, diagnostic criteria and measurement the following documents were recommended: the Valve Academic Research Consortium Consensus Documents on standardized endpoint definitions for transcatheter aortic valve implantation, guidelines by Akins et al (2008) for reporting mortality and morbidity after cardiac valve interventions, guidelines on the
Clinical performance outcomes	Function and quality of life (QoL) scores with a minimum of 2 years follow-up. "When documenting patient performance scores, it is recommended that manufacturers provide data with a minimum of two years follow-up post-surgery to reduce the risk of confounding due to procedure variables." Table 7 presents function and QoL scores for different joints that have been identified from systematic reviews and primary studies	10 key performance outcomes were derived from Health Canada, FDA guidance documents and systematic reviews on AICDs.	

	Joint prostheses	Active implantable cardiac devices (AICD)	Heart valves
			evaluation of prosthetic valves with echocardiography.p133,134 In addition to the recommendation on the minimum of outcomes to be reported clinical outcomes extracted from health technology assessments (HTA) were listed in Tables p134-136 Further the values from the guidance documents above for diagnostic criteria were listed in Tables p137-141.Values are indicative. In addition, study characteristics such as study design, sample size, follow-up and comparators were extracted from systematic reviews and HTA p143-146
Performance values	"Manufacturers should demonstrate that CPRs for a device or comparable device, if used to substantiate the safety and performance of the device, are equal to or better than published CPRs for joint prostheses of the same class as defined by the AOANJRR or another international joint registry (such as the National Joint Registry [England and Wales]), within the first two years of implantation at a minimum." Further, detailed requirements how to measure rates of revision p84		For surgically implanted valves objective performance criteria for clinical evaluation of new heart valve prostheses by ISO (Wu et al 2014) were recommended see Table p 142 A new valve should have complications rates lower than twice the OPC. "For transcatheter valves the number of events for each of the listed outcomes should be similar to or less than those reported in studies published in peer reviewed journals or heart valve registries for a similar type of prosthetic heart valve in the same valve

	Joint prostheses	Active implantable cardiac devices (AICD)	Heart valves
			position. Values that are reported need to be supported by clinical justification" p134-136
Surrogate outcomes	Adjunct data for surrogate markers for late revisions (after 2 years) can be provided. "Manufacturers, in selecting and reporting surrogate markers of safety, should provide a clinical justification for the selection and where Possible should use validated measurement tools." p84-85	Not mentioned explicitly	Not mentioned explicitly
MCID for function scores	Ideally, a minimum clinically important difference (MCID) for the scores should be defined and the success margin that can be used to evaluate clinical success. "When available, these values can inform the design of clinical trials and provide a minimum effect size to determine the necessary statistical power as well as the clinical interpretation of the data." Table 8 presents MCID for many of the scores shown in Table 7 p 87-88 Values are indicative		- An adaption of a rapid systematic review was performed. Search queries and searched databases are described, time of search 2009-June 2014, selection criteria were established a priori. No information on how many people selected by which algorithm and on data extraction methods reported. See section "Source material" p174-176
Methods for identification of outcomes	An adaptation of a rapid systematic review was performed. Search queries and searched databases are described, time of search 2009-June 2014, selection criteria were established a priori. No information on how many people selected by which algorithm and on data extraction methods reported. See section "Source material" p174-176		

AICD: active implantable cardiac device, AOANJRR: Australian Orthopedic Association National Joint Replacement Registry, ARC: Academic Research Consortium, CPR: cumulative percent revision, HTA: health technology assessment MDIC: minimum clinically important difference, MEDDEV: Medical Device Directives, OPC: objective performance criterion, VARC: Valve Academic Research Consortium.

Table 21. Recommendations from the TGA guidance on outcome measures for clinical investigations for specific medical devices. Part 2

	Arterial stents			Implants AAA repair	Implants PDA repair
	Coronary stents	Carotid stents	Peripheral stents		
Clinical outcomes	"Manufacturers are advised to use standardized definitions for clinical endpoints for coronary stents as defined by the Academic Research Consortium (ARC), in 2007. The ARC nominated clinical outcomes have been adopted by the European Commission in their guidance MEDDEV 2.7/1." A distinction between device-oriented and patient-oriented composite endpoints is provided, and that	As primary outcome the composite of death, stroke, or myocardial infarction Secondary outcomes included a mix of surrogate and final outcomes (7 listed), "Manufacturers are advised to use a validated stroke assessment tool e.g. the National Institute of Health Stroke Scale to evaluate patients pre- and post-procedure." Rates of adverse events across the literature	Outcomes were identified in a literature review. Outcomes include a mix of surrogate and final outcomes (9 outcomes listed) taken from trials in the systematic review evidence base patient follow-up based on the acute (< 48h), sub-acute (< 30days), late (< 1year) or very late (> 1 year) timeline are in line with the studies from the literature.	Outcomes were identified in a literature review. Evidence focused on AE, post-operative complications, all cause and disease-specific mortality. "Additional outcomes were a mix of surrogate and final outcomes" 14 outcomes listed p101. Definition of clinical success /failure by 7 outcomes Technical success is defined by 8 outcomes "Manufacturers should specify the time period for clinical success. Life table or Kaplan Meier estimates should not have standard deviations of greater than 10%. Any changes in lesion anatomy during follow-up should be referenced to	"Outcomes of primary interest were adverse events and the surrogate outcomes of primary success, residual shunt and need for blood transfusion."p102 "Manufacturers are advised to provide a justification for the selected clinical outcomes and values that define clinical and technical success." P102 Manufacturers are advised to demonstrate PDA closure rate at implant, 24 hours post-procedure and at appropriate clinical follow-up. Follow-up has been reported at 1, 2 and 5 years. Patient follow-up and assessment method should be supported with a clinical justification "Follow-up in the studies included in the systematic

	Arterial stents			Implants AAA repair	Implants PDA repair
	Coronary stents	Carotid stents	Peripheral stents		
	a clear definition and justification have to be provided when “major cardiac events” is used as endpoint. Evidence for clinical device success is demanded, definitions are provided. Patient follow-up should be reported for acute (0 – 2 hours), sub-acute (> 24 hours to 30 days), late (> 30 days to 1 year) and very late (> 1 year) events. These are in line with patient follow-up times in the literature presented in Tables p98-99.	are highly variable due to different populations, operator experience and technique, medical management goals and primary endpoints. An indicative example of AE rates is presented. “However, manufacturers are advised to provide a clinical justification of the event rates deemed to be acceptable for the target patient population in which the carotid stent is to be used.” A definition for procedural success is provided		measures taken immediately post-procedure.” patient follow-up based on the acute (< 48h), sub-acute (< 30days), late (< 1year) or very late (> 1 year) timeline are in line with the studies from the literature.	review examined for this report was unclear but was possibly 6 months. However, manufacturers are advised that follow-up should be reported for the peri–procedure period as well as late (≤1 year) and very late (≥ one year) time points.”

	Arterial stents			Implants AAA repair	Implants PDA repair
	Coronary stents	Carotid stents	Peripheral stents		
		Timepoints for patient follow-up as for coronary stents			
	An overview on outcome measures identified in clinical trials from the systematic review evidence base is provided. Data are indicative				
Performance values		-See above	"Generalized safety and performance values cannot be provided because of the heterogeneity in lesion anatomy and location, stent size, materials and associated stent technologies. Therefore, manufacturers are advised to: define the patient cohort and provide a		"The diversity of lesion size and heterogeneity of currently marketed devices for PDA repair limits the generation of generalized safety and performance values. Manufacturers are advised to provide a justification for the selected clinical outcomes and values that define clinical and technical success." Values for clinical success and for major adverse events have been reported in the literature and serve as a guide to

	Arterial stents			Implants AAA repair	Implants PDA repair
	Coronary stents	Carotid stents	Peripheral stents		
			clinical justification for selected safety and performance parameters, define the lesion anatomy according to a recognized classification system e.g. Transatlantic Inter-Society Consensus."		acceptable safety and performance for a PDA device.
Surrogate outcomes	Not mentioned explicitly	Mentioned, but no statement on validation	Mentioned, but no statement on validation	Mentioned, but no statement on validation	Mentioned, but no statement on validation
Methods for identification of outcomes	An adaption of a rapid systematic review was performed. Search queries and searched databases are described, time of search 2009-June 2014, selection criteria were established a priori. No information on how many people selected by which algorithm and on data extraction methods reported. See section "Source material" p174-176				

AAA: abdominal aortic aneurysm, ARC: Academic Research Consortium, MEDDEV: Medical Device Directives, PDA = patent ductus arteriosus.

Validity:

In this section on validity as a general issue of trial design, we focus on recommendations for dealing with bias to achieve an internally valid study design. Important aspects of validity were discussed with reference to the PICO scheme, so recommendations on choices to make regarding PICO that are intended to improve the validity of a CI, will not be repeated here. Instead, we deal with remaining issues contributing to internal validity beyond PICO, such as randomization and blinding, and with recommendations on how to judge overall validity for example by evaluating risk of bias.

Considerations on external validity (i.e. the generalizability of a study to the target population, consistent with the intended use of the MD) have also been covered, mainly in regulatory recommendations on the selection of the study population and study sites, and so they too will not be repeated here.

We included six guidance documents ([12], [14], [16], [19], [33], [38]). Two further documents, on Bayesian statistics [18] and adaptive study designs [22], also consider validity explicitly, but they are covered in the section on statistical methods.

The **MDCG 2020-6** guidance document on clinical evidence needed for legacy devices [38] defines the term "scientific validity" as used in the context of the MDR in reference to clinical data planning, evaluation and conclusions:

> "Embedded in the term 'scientific validity' are concepts including adequacy of study design and controls for bias, appropriateness and relevance of research questions, adequacy of sample sizes and statistical analyses, completeness of data, adequacy of follow up period, and appropriateness of conclusions on the basis of objective evidence. Section 9.3.1 of MEDDEV 2.7/1 rev. 4 provides guidance for the evaluation of methodological quality and scientific validity under the MDD/AIMDD which are equally valid under the MDR which can be considered to apply when referencing 'scientific validity' in this guidance."

The cited section in the **MEDDEV 2.7/1 rev. 4** document "How to evaluate methodological quality and scientific validity" [33] provides criteria for evaluators to examine:

> "the methods used to generate/collect the data and evaluate the extent to which the observed effect (performance or safety outcomes) can be considered to be due to intervention with the device or due to confounding influences (e.g. the natural course of the underlying medical condition; regression to the mean, concomitant treatments); bias; random error; inadequate disclosure of information; misinterpretation".

Sub-section a. lists items to consider regarding the design of pre- and post-market studies. Adequate selection of all PICO elements is mentioned. Regarding the study population, the distribution of prognostic factors in the study arms should be comparable. Regarding outcomes, issues that should be considered include adequate recording and reporting of SAE and device deficiencies, whether the follow-up period was long enough for outcomes to occur, whether measurement intervals were frequent enough to detect temporary side effects, and the reliability of methods used for quantifying symptoms and outcomes. Criteria that are mentioned for judging validity include prospective

randomization and blinding of patients, professional users and outcome assessors; adequate handling of concomitant interventions; and adequate sample size and power calculation.

There is a comprehensive treatment of the topic in the **FDA document** on design considerations of pivotal trials [19]. Its section 6.2 explains the statistical concept of bias:

> "Bias is the introduction of systematic errors from the truth. Bias can be introduced in subject selection, study design, study conduct, and data analysis procedures. In a clinical study, bias may lead to an incorrect determination of safety and effectiveness. Study designs that introduce little or no bias are preferable to designs that do not control for bias, which can be introduced into clinical studies due to a number of reasons." (6.2)

The challenge to avoid systematic errors in studies was behind the classification of study designs in the FDA document, so its recommended measures to minimize bias (randomization, blinding, use of concurrent controls, placebo/sham controls) have already been described (see sections 4.4.1) and will not be repeated here.

The guidance from **MHRA** on statistical considerations [12] also recommends blinding of investigators and evaluators "if this is practical", to avoid investigator bias, evaluator bias, and placebo effects. If it becomes necessary to break the code of assigned interventions, then that should be done by an individual who is not a member of the team caring for the patients or subjects. The guidance accepts that blinding during investigations of medical devices is often difficult or impossible.

> "Under the circumstances therefore, care must be exercised by the study staff to assure that these biases are minimized by assuring that the evaluator is blinded to the assignment of patients to a particular intervention or control group." (1.5)

The advantages of randomization "to produce device groups in which the distribution of prognostic factors, both known and unknown, are similar" are described. Randomization is not explicitly recommended, but advice is given about how it should be applied:

> "There are generally some advantages to be gained by randomizing patients in blocks. This helps to increase the comparability of the device groups throughout the period of allocation. It also provides a better guarantee that the device groups will be of nearly equal size."

For multi-center studies, it is recommended that the randomization procedure should always be organized centrally. Further it is stated that "it is often advisable to have separate randomization schemes for each center". To avoid facilitating predictability of group assignment, details of the randomization should not be contained in the study protocol, but "should be set out in an annex, which can be withheld from the study site." Also, "the randomization schedule itself should be filed securely by the applicant in a manner which ensures that blindness is properly maintained throughout the trial." But the possibility that the blind has to be broken for any patient in an emergency has to be taken into account (1.5).

The guidance document from the Japanese regulatory authority [16] mentions randomization and blinding only in passing, apart from the recommendation that a confirmatory study should desirably be randomized and blinded (3.1). In the section on "conduct of good clinical trials" it is stated that:

> "For randomization, an appropriate method shall be used to ensure objectivity of the randomization (methods hardly ensuring objectivity such as an envelope method is not recommended)."

In the **guidance document from TGA** [14], the general section on clinical investigation does not contain any recommendations regarding bias or validity, but this topic is considered in its section on "Clinical evaluation" under subsection "Appraisal of clinical data". One point to consider in appraisal is "determining the contribution of each dataset to the overall performance and safety profile of the subject device, considering the data generation/collection methods and potential sources of confounding or bias that may influence results".

Reference is made both to the concept of level of evidence, which classifies study types hierarchically according to their risk of bias (see 4.4.1), and to tools for systematically appraising the validity of a study, that are ordered according to study type. For randomized studies, the Jadad score is listed, and for randomized and non-randomized studies, the Checklist by Downs & Black. For additional advice on quality assessment tools, the guidance lists literature from organizations in the field of evidence-based medicine: the Centre for Evidence-Based Medicine, the Cochrane Collaboration, and the Scottish Intercollegiate Guidelines Network. Regarding appraisal, it is recommended to give preference to validated tools that are "appropriate for the data set in question, and [to] indicate which ones were used". Assessment of the risk of bias is demanded for outcomes (and not only at the level of the whole study) (page 32). The corresponding chapter on "Appraisal of clinical data" of MEDDEV 2.7/1 Rev 4 appendix 6 is mentioned, with reference to examples of studies that may lack scientific validity for the demonstration of adequate clinical performance and/or clinical safety (page 32).

The recommendations aim to guide appraisal of the risk of bias in a literature review of clinical studies, but these considerations also show relevant issues to take into account during evaluation of the validity of a clinical investigation. The TGA refers to methods developed for evidence-based medicine – it recommends that a randomized trial is the preferred study design. The section on specific devices (joints, cardiovascular devices to promote patency or functional flow, vascular heart valves, and implantable pulse generator systems) discusses which end-points to measure, and when and how. They all contribute to the validity of a study.

4.4.5 Statistical methods

We included 14 documents in this analysis ([12], [14], [15], [16], [18], [19], [21], [22], [23], [24], [26], [27], [33], [41]).

Two guidance documents from the FDA cover special statistical methods: one addresses the use of Bayesian statistics in trials for MD, and the other concerns adaptive trial designs for MD ([18], [22]). A third document, from MHRA, is also dedicated to statistical considerations for CI of MD [12]; it contains recommendations for important elements of study design such as PICO, and for the statistical analysis but without elaborating specific methods. The IMDRF document on clinical investigation [41] lists statistical considerations that should be pre-specified in the study protocol. Another two documents from the FDA, one on the evaluation of sex-specific data in MD studies [21] and the other

on the evaluation of age-, race-, and ethnicity data [24], deal with statistical aspects of subgroup analyses in relative detail. An FDA document on race and ethnicity [23] provides guidance how these data should be collected and categorized. The FDA strategic plan on "Health of Women" [27] sets a goal for the collection, analysis and reporting of sex- and gender-specific results. Subgroup analyses are elaborated in more detail in the other FDA documents.

The remaining guidance documents ([14], [16], [19], [26], [33]) make recommendations on single aspects of statistical analysis, mainly on calculating sample size or on pre-specifying study design and analysis.

In the paragraphs below, we first describe recommendations on general aspects of statistical analysis, then recommendations on the analysis of data from specific demographic subgroups, and finally recommendations on Bayesian statistics and adaptive study design.

4.4.5.1 Statistical uncertainty, sample size calculation, pre-specification of statistical analysis

The **guidance from MHRA** addresses a wide range of issues in statistical analysis. It emphasizes that "sample size justification is an important consideration when planning a clinical investigation" (1.2), and it specifies elements for sample size calculation "of the usual method" as follows:

> "specification of a primary variable, the null hypothesis, the alternative hypothesis, the probability of erroneously rejecting the null hypothesis (the type 1 error, conventionally 5% or less for a 2-sided test or 2.5% or less for a 1-sided test), the probability of erroneously accepting the null hypothesis (the type 2 error, conventionally 20% or less), the approach to dealing with drop-outs and other protocol deviations".

In non-inferiority and equivalence studies the choice of the non-inferiority or equivalence margin, which directly determines the sample size, has to be justified as well. Further, the study protocol should contain the method by which the sample size has been calculated "together with the estimates of any quantities used in the calculation and the source of such estimates". Sample size calculation should also make allowance for loss to follow-up and for the possibility that the treatment effect may be less than expected.

Pre-specification of data analysis in an analysis plan is considered as another important point in the design of a study, "since such factors may well affect the choice of what variables to collect and possibly other aspects of the study design". Three topics that should be addressed specifically are study population; missing values and outliers; and estimation, confidence intervals and hypothesis testing.

> "The analysis plan should first determine the population of patients whose data are to be included in the main analysis. As a minimum, documentation is required for all patients for whom study procedures were initiated and who have given their informed consent. The content of this patient documentation depends on detailed features of the particular investigation, but at least demographic and baseline data on disease status should be collected whenever possible."(2.1)

A requirement that is considered especially important for single-arm studies is that the outcome should be described for all patients who are identified as potential recipients of the MD, even when the MD was not used. The characteristics of both intention-to-treat and per-protocol analyses are described. For intention-to-treat analysis, objective entry criteria that will be used to exclude patients from analysis should be pre-specified and justified. Patient withdrawals before randomization should be reported "to allow assessment of the degree to which the patients who are included in the trial are a select subgroup of those who might have been included" (2.1). Section 4 of the guidance on follow-up emphasizes as well that all patients and devices that enter the CI should be accounted for, and reasons for exclusion carefully documented:

> "The effect of all losses of patients or of data, withdrawals from treatment and major protocol violation on the main analysis of the primary variables should be considered carefully. Patients lost to follow-up or withdrawn from device use should be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome."(4)

The section on missing values and outliers emphasizes that much effort should be undertaken to ensure a complete collection of data, to avoid bias. Outliers should be justified medically and statistically. If no procedures for dealing with outliers were included in the investigation protocol, then a sensitivity analysis should be performed with the actual values and compared with at least one other analysis eliminating or reducing the outlier effect. Differences between their results should be discussed (2.2).

Regarding effect estimation and uncertainty, the statistical analysis plan should specify the hypotheses to be tested, the device performance characteristics which are to be estimated, and the statistical methods that will be used to analyze primary and preferably also secondary variables. For effect estimates, confidence intervals should be provided wherever possible, together with how they were calculated. For tests of statistical significance, it should be indicated whether they are one- or two-sided. For one-sided tests the significance level should be set at half the conventional level used for two-sided tests (e.g. 2.5% in the case of 5%), and one-sided confidence intervals of 97.5% should be used if the significance level is 2.5%. Since non-inferiority trials use one-sided hypothesis tests, the significance level would typically be 2.5%. Further, the statistical approach to account for multiple testing should be included in the study protocol. For confirmatory studies multiplicity should always be considered (2.3).

In the section on the conduct and monitoring phase of a study it is recommended that any changes to the inclusion and exclusion criteria, and interim analyses with blinded data, are justified and documented in an amendment to the study protocol. This should also cover statistical consequences such as adjustments to the sample size or modifications to the analysis plan. The document states that the MHRA must be informed before any changes are made regarding inclusion and exclusion criteria or sample size.

The **guidance document of IMDRF** on clinical investigation [41] contains a section 6.0 on "General Principles of Clinical Investigation Design". This section has a part with statistical considerations which

should be prespecified in the protocol and "based on sound scientific principles and methodology". The following items are listed without further explanation:

- "clinically relevant endpoints
- analysis population
- statistical significance levels, power
- sample size calculation and justification
- analysis methodology
- management of potential confounding factors
- procedures for multiplicity control and adjustment of error probabilities
- procedures for handling of missing, unused or spurious data, including drop-outs
- procedures for handling deviations from the original statistical analysis plan

and, as applicable:

- accounting for learning curve issues
- specification of interim analyses
- specification of subgroup analyses" (6.0).

The **FDA guidance on design considerations for pivotal studies** [19] contains a separate section on "Study Analysis". In this document it is emphasized that:

> "the study protocol should have a detailed, pre-specified Statistical Analysis Plan that includes plans to evaluate, to the extent possible, key assumptions that were made in the design of the study (e.g. assessment of carry-over effects in a crossover study design, proportionality of hazards in a survival analysis, or pooling analysis across clinical sites or geographic regions). This predefined SAP should be adhered to in analyzing the data at the completion of the study to support the usefulness of the evidence generated by the study".

Sensitivity analyses should be pre-specified in the protocol to demonstrate that inferences drawn from study results are robust (9.3). The impact of missing values on the conclusions from the study should be analyzed (9.3). It is repeatedly pointed out that unplanned post-hoc analysis and deviation from the analysis population may endanger the validity of a study. Change of the primary endpoint and unplanned subgroup analysis are mentioned as examples for post-hoc analyses. It is conceded, however, that "in some cases, *post-hoc* analyses may complement pre-specified analyses, as long as they are clearly described and interpreted with the appropriate degree of skepticism that comes with this type of analysis" (9.3).

The **FDA guidance document** on "Consideration of Uncertainty in Making Benefit-risk Determinations in Medical Device Premarket Approval" (26), published in 2019, intends to enhance "transparency and consistency in the premarket review process by describing several factors that FDA considers in assessing the appropriate extent of uncertainty about a device's benefits and risks when reviewing these types of premarket submissions" (III). It lists factors that are used to set the level of uncertainty in a benefit-risk determination:

- the extent of the probable benefits of the device (type, magnitude, probability, duration and frequency) compared to benefits of already approved alternative treatments or standard of care;
- the extent of the probable risks of the device (severity, type, number, rates, probability, and duration) compared to approved alternative treatments or standard of care);
- the extent of uncertainty regarding the benefit-risk profile of approved alternative treatments or standard of care;
- patients' perspective on appropriate uncertainty;
- the extent of public health need (seriousness of disease, benefit-risk profile of available therapeutics, proportion of target population with positive benefit-risk-profile);
- feasibility of generating extensive clinical evidence pre-market;
- the ability to reduce or resolve remaining uncertainty post-market;
- likely effectiveness of mitigations such as labelling; [and]
- type of decision being made (Human device exemption vs premarket approval).

It is stated that the FDA would accept a higher degree of uncertainty of the benefit-risk profile in a premarket approval, in terms of the level of the type I error rate, if there are probable public health benefits from earlier patient access to the device (IV). Two circumstances are mentioned where greater uncertainty in premarket approval would be appropriate: break through devices and devices intended for small patient populations (V).

> "Further, it may be appropriate to collect additional data in the post-market setting, rather than premarket, to address the greater uncertainty about the device's probable benefits and risks, provided that the statutory standards for premarket approval are met ("premarket-post-market data shift"). This may depend, in part, on the magnitude of the probable public health benefit (e.g. a greater data shift could be appropriate if the probable magnitude of the benefit is high) and the likelihood that the data can and will be collected in a timely manner post-market (e.g. a large data shift may not be appropriate if post-market data collection is not likely to occur in a timely manner or at all)." (V.A)

The same approach could be applied to some devices which are intended to treat small populations of patients, particularly where:

> (1) "because of the rarity of the disease or condition, it is generally infeasible or highly resource or time intensive to generate extensive clinical evidence premarket; and
>
> (2) there is an unmet medical need that is addressed by the device, such as there are no available therapeutics or diagnostics for that patient population" (V.B).

Subsequently, hypothetical examples are given how "uncertainty may be reflected in the confidence level or one-sided significance level for a clinical study", but it is conceded "that uncertainty may also be reflected in other ways e.g. use of surrogate outcomes". Two examples for therapeutic devices are considered, one for breakthrough devices and one for small populations. The supposed study designs in both cases are one-arm studies with a performance goal as comparator.

How much uncertainty can be accepted in a premarket approval depends also on the extent of reliable and timely data collection in the post-market setting. The conventional case without post-market data collection would pre-specify a one-sided significance level of 2.5%. In case of modest uncertainty with modest post-market data collection as a condition for approval, the significance level would be raised to 5%, and in case of high uncertainty and substantial post-market collection using a robust collection mechanism such as a registry as condition of approval the significance level would be raised to 20% (V.C. pages 18, 22). In the example of the breakthrough device this would reduce the sample size for the premarket study from 535 to 385 and 125 patients (V.C. page 18). In the example of the device for small populations the same figures are 274, 128, and 65 patients (V.C. page 22).

MEDDEV 2.7/1. Revision 4 [33] contains appendix A6 with examples of studies that lack scientific validity. One section titled “Improper statistical methods” covers not correcting for multiple subgroup testing, and using statistical tests with assumptions about the distribution of data although that has not been tested, the distribution is not plausible, or data have not been transformed. Another section on “Misinterpretation by the authors” refers to “not correctly addressing lack of statistical significance / confidence intervals that encompass the null hypothesis” and in addition “effects too small for clinical relevance” (A6).

The **guidance document of TGA** [14] makes statements only on sample size, in both its general and specific parts. The general statement is limited to the fact that studies which are not statistically powered “are generally considered poor quality” (page 29). The document lists the “IMDRF Sample Appraisal Criteria for Data Contribution” checklist. One item on statistical significance reads: “Has a statistical analysis of the data been provided and is it appropriate?” but it does not specify what is considered appropriate. Further, the guidance directly integrates Appendix 6 of MEDDEV 2.7/1 Rev 4 (on appraisal of clinical data) which gives examples of studies that may lack scientific validity (from page 32). In the device-specific parts, sample sizes for heart valve studies are recommended, referring to ISO 5840. For studies of joint prostheses, it is noted that minimally important clinical differences can be used to calculate the sample size.

Regarding statistical analysis, the **guidance of the Japanese regulatory authority** [16] addresses only sample size, which “should be established based on a statistical rationale”. A statistical rationale is not considered necessary for a feasibility study, however, and if it is difficult to recruit patients with a rare disease the study size “may also be determined through an in-depth discussion with experts in the field” (3.2).

4.4.5.2 Analyzing subgroups

We included four guidance documents on subgroup analyses ([15], [21], [23], [24]).

Health Canada makes some recommendations on the principles of subgroup analyses in its guidance on the inclusion of women in clinical trials and on the analysis of sex differences, in clinical investigations of pharmaceuticals, but it states that sex-specific analyses should also be carried out for MD (2.6). It is recommended that:

> "the statistical section of the study protocol for Phase III trials include pre-specified plans for assessing sex related differences on efficacy and safety. The prespecified plans for assessing such differences should be carried out once the overall treatment effect has been shown to be significant. Post hoc analysis to assess sex related differences should only be carried out in trials that are already completed or ongoing, and the analysis should be labeled as post hoc. In addition, if there are scientific reasons to suggest the potential existence of sex related differences, stratification by sex at the study design stage should also be considered" (2.2).

It is stated that "it is important to confirm the reasons for these differences […] in order to determine how to mitigate the effect of sex-related differences in the clinical setting" (2.2). This means that explaining factors for the differences should be identified.

Two **documents from the FDA** ([21],[24]) describe the evaluation and reporting of specific data by sex, age, race and ethnicity, in MD clinical studies. Regarding statistical concepts for assessing heterogeneity (i.e. differences in outcome across subgroups) the second document [24] refers to the methods described in the guidance on sex-specific data. Recommendations for subgroup-specific statistical design and analysis are presented in the appendix 1 "Decision framework" which is included in both guidance documents. Also, in both, section V gives detailed explanations of the recommendations.

The decision framework can be used when there is a hypothesis that there may be a meaningful subgroup difference in benefits and risks of treatment by the MD. We use the figures in the document on age-, race- and ethnicity-specific data, because it is more recent (2017) and it contains an additional figure with recommendations on reporting subgroup-specific results [24] (page 32) (see in Appendix of this report Figures from Appendix 1 in the FDA guidance on evaluation and reporting of age-, race- and ethnicity-specific data in medical device clinical studies (24)). In Figure 1 in the appendix, general recommendations are made for the statistical design of different study types.

During the planning phase for all study types, previous studies and data should be analyzed to assess if they suggest a meaningful difference by subgroup, and to identify any relevant covariates. Data about those covariates should be collected and used in a modelling approach to investigate the extent to which they can explain any observed differences. This approach, reporting by subgroup, and the strategy for assessing heterogeneity, should all be pre-specified in the study protocol.

Further issues in all studies are how to control the overall type I error rate, if multiple claims are sought, and how to power studies for subgroup-specific claims (V.B):

- In randomized studies, subgroups could be used as stratification variables.
- In one-arm studies, subgroup-specific OPC or PG might be considered.
- For comparative studies, the method for testing heterogeneity of treatment effect is to apply statistical hypothesis tests for treatment by subgroup interaction (V.A) for primary safety and effectiveness endpoints, and key secondary endpoints at the primary follow-up endpoint (V.C).

The null hypothesis of common tests for interaction is the absence of 'treatment by subgroup' interaction. It is important to distinguish between qualitative and quantitative interactions – qualitative interaction means that the therapy is harmful for one subgroup but beneficial for another, while quantitative interaction means that there is only a quantitative difference between subgroups and the direction of the effect is the same. The FDA points out that tests for interaction may have limited power, and that:

> "lack of statistical significance for a test of treatment by sex interaction may not convincingly evidence the absence of clinically relevant interaction. By the same token, moderate statistical significance may not convincingly evidence the presence of clinically relevant interaction".

In such cases, discussion with the FDA is advised (Figure 3 in the guidance, second footnote). The sequence of testing hypotheses in all subjects, implementing a strategy to control Type I errors, and then performing interaction tests for subgroups, must be pre-specified. The FDA recommends that tests for interaction should only be performed in the case of a statistically significant and clinically meaningful treatment effect. Figure 3 shows decision rules, and indicates when data from subgroups can or cannot be combined. In the case of statistically significant differences, it is critical to consider whether they remain after adjustment for covariates, and whether they are also clinically meaningful (V.C). Justification must be provided for any combining of data.

For single-arm studies, tests for interaction cannot be applied because there is only one treatment. Instead, hypothesis tests comparing different subgroups can be performed (V.A). Adjustment for covariates is recommended (V.C). The overall type I error rate has to be maintained by taking into account the multiplicity of testing (V.B). Methods for adjustment are not mentioned.

How subgroup analyses should be reported for a submission, is described in Figure 4 of the FDA guidance (24). We summarize those recommendations here, because of their connection with statistical analysis.

Recommendations are given separately about how to report characteristics of the enrolled study population and how to give information about outcomes. For the former, a description of proportions by subgroups and comorbidities, whether the proportions enrolled are consistent with prevalence, and a comparison and discussion of subgroup differences between baseline and follow-up, should be described. For the latter, if no clinically meaningful subgroup differences were found then that should be stated, and the analyses should be described. If there was a clinically meaningful but not statistically significant difference, the findings should be reported descriptively with a discussion about how clinically meaningful differences may contribute to differences in the benefit-risk profile in certain subgroups. If the differences are clinically meaningful and statistically significant, the outcomes should be reported by subgroup. If subgroup analyses were not pre-specified, then only descriptive statistics should be used. Any methods used for statistical subgroup analyses should be clearly stated (Figure 4 of FDA document).

Besides the decision framework for statistical analyses of subgroup differences, the guidance also contains recommendations for the categorization of age. It is stated that standardized age categories may not appropriate for all devices, but "more discrete age groups should be considered" (III.B). Age

groups should be given specific years, not just classified as " older" and "younger". The pediatric population is defined by U.S. regulation as any patient less than 22 years of age, and subdivided into four subgroups by another FDA guidance document on “Premarket assessment of pediatric devices”, published in 2014 (80). The FDA document does not define a specific age range for an elderly population, due to the wide variety of medical devices, but it states that relevant disease characteristics should be used for categorization (III.B.1). For categorization by race and ethnicity, it is recommended to use the FDA guidance on collection of race and ethnicity data in clinical trials (23), but it is acknowledged that “other ethnic and racial categories may be appropriate depending on the study population”. The methods of identification and the categories should be defined in the study protocol (III.B.2).

4.4.5.3 Recommendations for specific statistical and design approaches

The Bayesian approach to clinical studies

The **FDA** dedicated one **guidance document**, published in 2010, to the use of Bayesian statistics in CI for MD [18]. The Bayesian approach is described as follows in section 3:

> “The Bayesian paradigm states that probability is the only measure of one’s uncertainty about an unknown quantity. In a Bayesian clinical trial, uncertainty about a quantity of interest is described according to probabilities, which are updated as information is gathered from the trial.” (3.2)

Before the trial starts, a probability distribution is given to all the possible values of interest. The probabilities may be “informative” i.e. the “distribution gives preference to some values of the parameter of interest as being more likely than others” (4.5). For example, the distribution may come from former trials, or it may be “non-informative” i.e. each value in the distribution has the same probability. The probability distribution estimated before a trial is started is called the prior distribution.

> “After data from the trial become available, the prior distribution is updated according to Bayes’ theorem. This updated distribution is called the posterior distribution, from which one obtains the probabilities for values of the unknown quantity after data are observed. […] Bayesian inferences are based on the posterior distribution. For example, a Bayesian decision procedure might rule out a set of parameter values if the posterior probability of the parameter values (given the observed data) is small.” (3.2)

> “The final objective is to obtain the posterior distribution, the probabilities of the possible values of the parameter θ conditional on the observed data, which can be denoted in symbols as P(θ| data). Bayes’ theorem is used to update the prior distribution for θ, P(θ), via the likelihood, P(data|θ), to obtain the posterior distribution for θ, P(θ|data). The information about θ is summarized by this posterior distribution, and Bayesian inferences are based on it.” (3.5)

4.4.5.4 Choice of a Bayesian approach

There is no direct recommendation in the guidance document on Bayesian statistics [18] about when to prefer Bayesian to frequentist statistics in trial design, but advantages and challenges of Bayesian designs are explained in sections 2.2, 2.6, and 2.7. Bayesian statistics can use prior information from former studies. Due to the evolutionary, incremental development of MD, where previous generations of a device with minor modifications may predict the effect of the modified device, such prior information may be a justification for a smaller-sized or shorter-duration pivotal trial. Even without prior information the Bayesian approach can be used for adaptive trials, where pre-specified changes can be implemented during a trial with interim analyses, for example to adapt sample size or chance of randomization schemes. "Other potential uses include adjustment for missing data, sensitivity analysis, multiple comparisons, and optimal decision making"; as potential benefits of using Bayesian methods, the following arguments are given [18]:

1. by the incorporation of prior information into a current trial the information is augmented, and the precision may be increased. "The Bayesian analysis brings to bear the extra, relevant, prior information, which can help FDA make a decision."
2. the use of prior information may reduce the necessary sample size in some instances, and in case the prior information does not agree with the results of the current trial, the Bayesian analysis would be conservative compared to the frequentist analysis.
3. adaptive trial designs may be easier to implement with a Bayesian approach.
4. "With appropriate planning, the Bayesian approach can also offer the flexibility of midcourse changes to a trial." This includes dropping unfavorable treatment arms and modifications of randomization schemes. The latter may be "particularly relevant for an ethically sensitive study when enrollment becomes problematic for a treatment arm".
5. Bayesian approaches may allow for an exact analysis, when the frequentist approach is only approximate or too difficult to implement.
6. Bayesian methods allow for great flexibility in dealing with missing data and approaches to multiplicity (e.g. inferences on multiple endpoints or multiple subgroup analyses).

These potential challenges are mentioned:

1. the need for extensive preplanning. In addition to the usual planning of design, conduct, and analysis of a frequentist trial, it has to be decided already at the design stage on the prior information to use, the information to be obtained from the trial and the mathematical model used to combine the two. Because different choices on these issues can lead to different results, a Bayesian trial in the regulatory setting needs pre-specification and agreement on both the prior information and the model. Therefore, a formal agreement meeting especially on the identification of prior information may be appropriate. Even when the FDA agreed beforehand on the choices regarding prior information, the FDA advisory board may question the prior information. Good preparation to justify the choice clinically and statistically and performing sensitivity analyses to check the robustness of the model are recommended.

2. because the Bayesian approach can involve extensive mathematical modelling, the modelling choices should be made in close collaboration with the FDA.
3. the Bayesian approach often involves specific statistical expertise in Bayesian analysis and computation.
4. Bayesian terminology is not yet commonly used, this may be challenging in expressing trial results in a way easy to understand.
5. the flexibility and complexity of Bayesian models create greater possibility for errors and misunderstandings.
6. Bayesian and frequentist approaches may differ in the conclusions of a trial but switching post hoc is not scientifically sound.

4.4.5.5 Specific issues in designing a Bayesian clinical investigation

The essential steps in planning a Bayesian study are presented in section 4 of the FDA document, which states that fundamentally they are same as for other clinical investigations (4.1). Sections 4.2 to 4.4 describe how to determine the elements of PICO (as summarized above in paragraph 4.3.6 of this report).

We consider here the recommendations on issues that are more specific for Bayesian studies – such as the choice of the prior distribution, hierarchical modelling, and the use of sample sizes that are not fixed at the beginning of the trial – which are described in sections 4.5 to 4.8 in the guidance document [18].

For *choosing sources of prior information, the* FDA recommends identifying as many sources as possible (e.g. clinical trials conducted overseas, patient registries, clinical data on similar products, pilot studies). Because "goodness" of prior information is subjective, the choice of prior information should be discussed with the FDA before a study begins. The guidance states that prior information from previous studies is the easiest to evaluate. It is recommended that the studies used to construct the prior should be similar to the current study regarding the study protocol (PICO etc.) and the time frame of data collection, to ensure that the practice of medicine and the study population are comparable. The included studies should also be representative of the results (positive and negative findings) and of reasons for inclusion and exclusion. Prior distributions based on expert opinion rather than data can be problematic because advisory board members may not agree with the opinions (4.5).

Hierarchical models can be used to combine multiple studies to obtain effectiveness and safety parameters. This is sometimes called "borrowing strength"; "the amount of strength borrowed can be translated into sample size" (4.6) and depends on the similarity of results between previous studies and the current study.

> "In a regulatory setting, hierarchical models can be very appealing: They reward having good prior information on device performance by lessening the burden in demonstrating safety and effectiveness. At the same time, the approach can protect against over-reliance on previous studies that turn out to be overly optimistic for the pivotal study parameter." (4.6)

It is pointed out that statistical adjustment for differences in prognostic or demographic covariates may be necessary, to achieve exchangeability between studies which is the presumption in the hierarchical model. Generally, proper calibration needs individual patient-level data, so the same covariates must be available for the current study as for the previous studies with which it is compared (4.6).

In contrast to the *sample size determination* of traditional frequentist trials, the sample size of Bayesian trials does not have to be fixed in advance. Instead, a particular stopping criterion (e.g. a sufficiently narrow credibility interval) may be pre-specified:

> "Because the sample size is not explicitly part of the stopping criterion, the trial can be ended at the precise point where enough information has been gathered to answer the important questions."

Regarding the sizing of a Bayesian trial, the FDA recommends (section 4.7):

1. a minimum sample size according to effectiveness and safety endpoints should be determined.
2. a minimum level of information from the current trial should be included to verify model assumptions and appropriateness of prior information used.
3. when hierarchical models are used a minimum sample size for determining the amount of information that will be borrowed from other studies.
4. the maximum sample size should be defined according to economical, ethical, and regulatory considerations.

Planning for a Bayesian trial design should include *assessment of the operation characteristics*: Type I error rate, type II error rate, power, sample size distribution and expected sample size, prior probability of claims for the device, and if applicable the probability of stopping at each interim look.

It is stated that the FDA considers type I errors together with other operational characteristics. An adequate characterization may need extensive simulations. Further it is pointed out that it may be appropriate to control for a type I error at a less stringent level when prior information is used, compared to a situation without using prior information, but the degree to which the level might be relaxed is a case-by-case decision by the FDA. It may recommend discounting of historical prior information if that is too informative relative to the current study. This consideration is also a case-by-case decision. In the Bayesian approach, hierarchical modelling considering subgroups as exchangeable can also be used to perform subgroup analyses and to adjust for multiplicity. The guidance states that such Bayesian adjustments may be acceptable to the FDA, "provided the analysis plan has been pre-specified and the operating characteristics of the analysis are adequate". Early consultation with the FDA in regard to the statistical analysis plan is needed (4.9).

4.4.5.6 Specific issues in the analysis of a Bayesian clinical investigation

In section 5 the guidance describes which trial findings should be defined, and partly how they should be analyzed. It recommends summarizing "the posterior distribution with a few numbers (e.g.

posterior mean, standard deviation, credible interval), especially when there are numerous endpoints to consider. FDA also recommends you include graphic representations of the appropriate distributions."

The posterior distribution contains all information from the prior distribution combined with the results from the trial (5.1). For Bayesian hypothesis testing, the posterior distribution may be used to calculate the probability that a particular hypothesis is true, given the data (5.2). Bayesian interval estimates called credible intervals are calculated from the posterior probability that an endpoint lies in this interval (e.g. 0.95 for a 95% credible interval). Reporting credible intervals in labelling is strongly encouraged (5.3).

The use of predictive probabilities is also specified. A predictive probability is the posterior probability of unobserved outcomes, future or missing, given what has already been observed (3.6). It is stated that such predictions" are reasonable only if you can assume the patients who have not been observed are exchangeable with the patients who have. This assumption is difficult to formally evaluate but may be more plausible in some instances (e.g. administrative censoring) than others (e.g. high patient drop-out)."

Predictive probabilities can be used to stop a trial for success or futility, to predict outcomes for future patients, to predict or impute missing data and adjust trial results, and to predict a clinical outcome from earlier measurements. The FDA recommends that the utility of predicting outcomes for future patients should be considered, as well as whether details should be included in the device labelling; it could help physicians and patients to make decisions regarding options for treatment.

If a prediction model is used for the imputation or adjustment of missing data, "the adjustment depends on the assumption that patients with missing outcomes follow the same statistical model as patient with observed outcomes." A sensitivity analysis should be performed using the prediction model, if an assumption of exchangeability or randomly missing data is questionable (5.4).

Interim analyses have to be pre-specified in the study protocol, and the methods should be agreed in advance of the trial. Two options are described: one applying the posterior probability of a hypothesis at the interim look, whether it is large enough, and the other using the predictive distribution for patients yet to be measured. If the predictive probability for success is sufficiently high, the trial may be stopped early, if the predictive probability is very low, the trial may stop early for futility (5.5).

All-important assumptions for the statistical model should be investigated (5.6) and deviations should be submitted in a sensitivity analysis. Items that may be investigated are listed: deviations from distributional assumptions, alternative functional forms for the relationships in your model, alternative prior distributions, alternative "hyperprior" parameters in hierarchical models, or deviations from any "missing at random" assumptions for missing data (5.7). For the development of an interim analysis plan, decision analysis may be used to determine the optimal value of the posterior probabilities to stop or continue the trial (5.8).

Adaptive study designs

Adaptive study designs may be used with Bayesian or with frequentist statistical methodology. The FDA published a guidance document about both types of adaptive designs for MD clinical studies, in 2016 [22]. An adaptive design is defined as:

> "a clinical study design that allows for prospectively planned modifications based on accumulating study data without undermining the study's integrity and validity"(22).

The FDA document describes the advantages and challenges of adaptive trial designs, in sections 2.C and 2.D, and it explains when to choose an adaptive design, in section 3.

4.4.5.7 Choice of an adaptive design

At least seven advantages of an adaptive design are given, compared to a non-adaptive design [22] (2.C):

1. "It can be more efficient, saving time, money, and resources". For example, a trial with preplanned interim analysis could be stopped early for success or futility, or a "trial with two or more investigational arms could plan to drop one of them based on accumulating data".
2. "Adaptive designs can improve the chance of trial success by employing sample size reassessment (SSR), whether for a superiority or a non-inferiority study" [22]. A planned SSR could adjust sample-size if the trial would otherwise be underpowered "where there is a treatment effect that is meaningful but smaller than originally anticipated".
3. In the regulatory setting, where some uncertainties on safety or effectiveness may be answered by post-market data instead of during premarket approval [81], "adaptive design may facilitate transition from premarket to post-market follow-up" (2.C).
4. In some cases, with sufficiently strong blinded treatment groups, planned modifications will not inflate the false positive error rate.
5. Certain types of adaptive designs can increase the probability that a patient is assigned to the treatment most likely to result in a better outcome for the patient and can thus enhance patient protection.
6. The patient population can be modified during the study to a more targeted indication, and thus prevent a failed study.
7. "Adaptive studies can improve decision-making at milestones during product development or increase the chance of a successful study with the potential to improve time-to-market. Overall, adaptive designs may enable more timely device development decision-making and therefore, more efficient investment in resources in a clinical study. From an ethical standpoint, adaptive designs may optimize the treatment of subjects enrolled in the study and safeguard their welfare from ineffective or unsafe treatments and interventions at the earliest possible stage." (2.C)

These possible limitations are mentioned:

- Preplanned modifications may require more effort at the design stage.
- If not correctly done, adaptive designs may introduce operational or statistical bias.
- Changes due to adaptation may lead to different results before and after the adaptation, which may confound the interpretation, [and]
- The maximum sample size or study duration may be greater than in a non-adaptive design [22].

In section 3 is recommended that when considering choosing an adaptive design, it should be checked whether an adaptive design is feasible and whether it is more appropriate as a non-adaptive design.

An adaptive design is considered feasible "if there are a small number of endpoints on which the adaptation will take place, and if the timing of the primary outcome is such that there is time to implement the adaptation if required" (section 3). An adaptive design may be less suitable in studies with multiple primary and secondary endpoints, when proper statistical control of Type I errors might be difficult. When the sample size is driven primarily by safety concerns, sample size adaptation on effectiveness endpoints will not be feasible.

When planning a pivotal study, consideration should be given to whether an adaptive design is advantageous. For this the recommendation is to select several realistic scenarios, some more and some less optimistic. For each scenario and adaptive design, the chance of success, the operating characteristics (probability of Type I error, and statistical power), and the average sample size should be calculated, and they should be contrasted with the characteristics of a non-adaptive design. If the assumptions about parameter values on which a sample size calculation is based are uncertain, for a non-adaptive study design, then an adaptive design may be preferable. If there is almost no knowledge about the parameter, an adaptive design may be inefficient, and a combination of feasibility and pivotal studies might be an alternative. The concept of "anticipated regret" is mentioned as a decision tool, that could be used for decisions. This concept tries to anticipate which study outcomes might lead to a failure of the study, and to identify what planning decision one might regret, and then plan to adapt during the study (e.g. to adjust for too small a study size) [22].

4.4.5.8 Validity issues in adoptive studies

Section 4 explains the threats to scientific validity implicit in design adaptations. The principles for adapting the design to ensure the validity of the scientific evidence are firstly to control Type I errors and maintain statistical power (1–Type II error), and secondly to minimize operational bias i.e. an influence on the ongoing operations of the study which might emerge by knowing the results by treatment group from the interim analyses.

The risk of Type I errors (false positive conclusions) is inflated by analyzing study data multiple times, by analyzing multiple endpoints, by comparing multiple subgroups, or by an increase of sample size. If such analyses are preplanned, then the Type I error can be controlled and the statistical power (1–Type II error) calculated. Analytical statistical methods and simulations can be used to obtain operating characteristics (i.e. Type I and 1–Type II error). The FDA recommends to "control Type I error and maintain adequate power for all study designs" [22] (pages 13-14).

Operational bias cannot be overcome by statistical adjustments. Thus "it is vital that standard operating procedures be followed to insulate information from study sponsor and investigators" (page 14), if designated study analysts have access to the overall unblinded results during the conduct of the adaptive trial. Further, safeguards must be in place "to ensure that those with legitimate access to unblinded data do not share information about these data with others" (page 15). Because operational bias is a major concern in adaptive trials, "one should limit the access to outcomes by coded or unblinded treatment groups" (section 10, page 35). Firewalls can be set up to "guarantee that access to such data is restricted only to those for whom it is absolutely essential". In addition, "it is recommended that the precise details of the adaptation algorithm are separated from the investigator-shared protocol and placed in a detailed statistical analysis plan" (page 36). This should reduce the ability of study observers to deduce the interim study results based on the knowledge of the adaptation protocol (page 36). Also information about the changes implemented after the interim analysis should be controlled, "so that only those who must have access to it know about the trial modification […] In the conduct of an adaptive design, an effective and well-documented firewall increases the likelihood that trial modifications will be scientifically valid, maintain integrity of the data and trial, and be acceptable for regulatory purposes" (page 37).

The Data Monitoring Committee (DMC), which has the task to safeguard trial participants, should have enough expertise and experience to oversee an adaptive study design, even when others are charged with the logistics of the adaptation. The protocol should clarify the role of the DMC in the conduct or analysis of adaptation. If the DMC recommends changes to the adaptive design, after it has had access to outcomes, that might imperil the scientific integrity of a study (pages 35-36).

Regarding unplanned changes to pivotal clinical studies, the FDA distinguishes between the situations in which outcome data remain blinded, and in which outcome data are unblinded. In the case of still blinded outcome data, in principle scientifically valid modifications might be possible. In the case of unblinded outcome data, the scientific integrity of the study may be endangered, and sponsors are strongly encouraged not to implement such changes (Section 7, pages 26-27).

4.4.5.9 Overview of Adoptive Study Designs

Table 22 presents an overview of adaptive design types or elements using blinded or unblinded data, their advantages and disadvantages, and measures to ensure the validity of the study, summarized from different sections of the FDA guidance document.

Table 22. Overview of adaptively designed studies summarized from sections 5, 6 and 7 of FDA guidance on adaptive study designs [22]

Design / type of adaptation	Description	Advantages / disadvantages	Methods to ensure validity
Adaptations using unblinded* data			
Group sequential designs	No fixed sample size / 1 or more interim analyses of outcomes by treatment group,	Uncertainty about enrolment at the beginning /possible operational bias after	Prospective planning, pre-specified statistical plans that account for interim analyses and

Design / type of adaptation	Description	Advantages / disadvantages	Methods to ensure validity
	possible early stopping for success or futility Bayesian or frequentist	decision to continue study after interim analysis, because inference on effect size possible by personnel	appropriate adjustments to significance level alpha, predetermined number of interim analyses with prescribed fraction of alpha spent at each look or pre-specified alpha-spending approach with function for spending alpha at various time points with flexible number of interim looks. Data analysis by Data Monitoring Committee in secure and confidential manner
Sample size reassessment (SSR)	One or more interim analyses to potentially adjust the sample size according to the comparison of the unblinded treatment group results, control of Type I error rate depends on sample size adjustment methodology and preplanned analysis that is used to combine the data from before and after the adaptation	Can help avoid underpowering studies. While the effect size is unknown at the start, if the expected range is narrow, a SSR strategy is preferable to group sequential design, otherwise group sequential design more efficient	Analytical calculations or computer simulations can guide choice of optimal time points for reassessment Clinical important effect size must be pre-specified
Bayesian sample size adaptation	Bayesian hierarchical models are used to combine data from a current study with prior data. Sample size is adjusted as information accumulates. At the interim analyses predictive probabilities can be calculated and also be used to stop for early success or futility, if	Inclusion of prior information can reduce sample size	Simulations are needed to determine the threshold values of predictive probabilities to stop for early success, futility or stopping recruitment.

Design / type of adaptation	Description	Advantages / disadvantages	Methods to ensure validity
	a pre-specified values are reached.		
Group sequential design with SSR	Interim looks to stop early for success and for SSR to increase according to pre-specified plan	-	-
Dropping a treatment arm	In studies with more than one experimental arm, arms could be dropped based on poor effectiveness	Can increase study efficiency, focus on aspects the are most likely to prove beneficial and successful	-
Changing randomization ratio	Response adaptive randomization changes randomization ratio between control and treatment group based on treatment outcomes	Can mitigate ethical concerns by reducing probability that patients receive less effective treatment Can improve study efficiency, can facilitate investigator and patient enrolment, but leads sometimes to slightly larger trials	-
Investigating both superiority and non-inferiority	To plan a study to investigate both superiority and non-inferiority		Two strategies may be used: 1. Planning a superiority study designed to investigate non-inferiority if the superiority hypothesis fails. Non-inferiority margin must be pre-specified and agreed upon before unblinding, SSR could be planned with change in claim 2.Planning a non-inferiority study, switch to superiority needs no further preplanning, because superiority margin already

Design / type of adaptation	Description	Advantages / disadvantages	Methods to ensure validity
			predefined, but additional SSR should be prespecified
Adaptive enrichment	Use of unblinded data, at one or more interim looks, to analyze pre-specified patient subgroups that might have differing responses to the experimental device.	Such analyses could be used in a preplanned way to modify the inclusion/exclusion criteria after an interim analysis	In all cases it is important that the chance of erroneous findings (the overall probability of a Type I error) be well-controlled in a prospective manner
Adaptation based on total information	The stopping rule is based on a pre-specified amount of information in the unblinded data, usually measured in terms of the variance of the primary endpoint.	Study is always correctly powered, no statistical penalty for repeated looks. Could be particularly helpful in single-arm studies	Pre-specified stopping rule must be strictly adhered to, to control Type I error
Adaptation of device or endpoint	A preplanned device or endpoint adaptation	Are rare in pivotal studies, but unplanned changes are common in feasibility studies	For planned changes, changes should be pre-specified, or types of changes anticipated and accounted for in statistical analysis plan
Seamless studies	A feasibility investigation that smoothly transitions to a pivotal study in a preplanned manner, if no significant changes to the device or study are made. If study is designed "inferentially seamless all data may be included in final analysis	Example: feasibility portion of the study includes several device configurations, only the most favorable configuration would be continued in the pivotal stage	Prospective study planning to combine the feasibility and pivotal study phases should occur before the feasibility data are accessed in an unblinded manner; the plan needs to control the overall Type I error for the combined two stages
Adaptive designs for safety endpoints	Focus on safety endpoint, to demonstrate that SAE rate is lower than a threshold.	-	Preplanned rule would need to demonstrate that it controlled for erroneous conclusion that SAE rate is at most the threshold

Design / type of adaptation	Description	Advantages / disadvantages	Methods to ensure validity
	Group sequential design with early termination rule		
Adaptive designs for open-label randomized studies	Adaptation after interim analysis in a randomized study without blinding of medical staff, patients, outcome assessors	Open-label study presents additional difficulties with operational bias	Pre-specified adaptations and detailed anticipation of all possible intended changes and corresponding adaptations, with appropriate checks of Type I error in the study protocol
Adaptive design for one-arm studies with OPG	Adaptation in treatment arm after interim analysis	Additional biases may be introduced by a one-arm study	A pre-specified adaptive design might be possible, knowledge of outcome data must be carefully restricted, a screening log of all incomers at each clinical site to ensure that no overt selection occurred
Adaptations without need to break blind*			
Covariate adaptive randomization	Using aggregated (still blinded) data for adaptation Examples: 1. Use of accumulated baseline data to provide better balance between two groups 2. to power a time-to-event study to the total number of events, not number of patients 3. calculate the overall variance for a continuous endpoint and make sample size adjustment on the hypothesized difference in the means	Use of aggregate data do not pose difficulty with Type I error control or bias. If blind is maintained in principle changes could be made during the study is conducted.	For example 2 and 3 the required amount of aggregate information to be used is determined in advance and study is continued until the amount of information is obtained. For changes not preplanned, it must be demonstrated that there was no access to any unblinded data, and that access to the data has been safeguarded.

Design / type of adaptation	Description	Advantages / disadvantages	Methods to ensure validity
Adaptive designs for observational comparative studies	Observational studies may have historical or concurrent non-randomized control, comparison of baseline covariates in the treatment group in interim analysis adaptation of control group and/or sample size		Comparison should be pre-specified and performed in a manner such that the personnel who conduct the comparability evaluation are blinded/masked to outcomes of all arms

OPG: objective performance goal, SSR: sample size reassessment.

* Unblinding / breaking blind means having access to outcomes by treatment group. "It does not mean that one cannot know: 1) the demographic breakdown of the groups, 2) the overall combined outcomes if there are two or more groups, or 3) which subjects are assigned to which groups (as long as the outcomes by subject or by group remain masked or blinded)." (22) (at page 15)

4.4.5.10 Specific issues in the statistical analysis of adaptive studies

In section 9 in the FDA guidance document [22] it is stated that naïve point estimates of treatment effects in adaptive trials are frequently biased, even when the Type I error is well controlled. Efforts to adjust for this bias can be prospectively planned in the statistical analysis plan, but methods of how to make adjustments are not mentioned. Whether important aspects such as study participants, device performance, and outcomes are different before and after the modification, should be analyzed. If an observed difference was unexpected, it might be an indication of operational bias. If no adaptations are made in what was designed as adaptive study, it should be analyzed according to its pre-specified statistical analysis plan.

4.4.6 Contextual factors and learning curve

We included four guidance documents with recommendations on contextual factors and learning curves ([14], [19], [33], [41]).

The **guidance** on design considerations for pivotal clinical investigations for MD from the **FDA** explicitly addresses special considerations for clinical studies of devices (4.2). Two that are particularly relevant to implantable devices, are the skill level and training of the user required to use the device in an effective and safe manner, and the learning curve associated with use of the device. It is stated that:

> "the skill sets of study investigators and personnel should reflect the range of skills of personnel likely to use the device in the intended use setting after marketing approval. The training provided to study investigators and personnel in the appropriate use of the device should guide the training that will be provided to users when the device is marketed. If no training will be provided for a marketed device, study personnel should not be specifically

> trained in the use of the device in order to ensure that the study reflects intended use conditions".

In the glossary, the learning curve is defined as:

> a "graphical representation of the change in the rate of learning in the use of a medical device or, for a surgical implant, in the implantation procedure of the device. It can be measured in terms of the time taken to achieve desired outcomes or in the number of procedures until successful outcomes are assured".

It is stated that devices with steep learning curves may not be suitable for some settings, and that for some devices the learning curve could be determined during the exploratory stage. A learning curve in a pivotal trial should be addressed in the study protocol. It should be clearly defined which subjects are part of the learning curve period, and how its results will be reported in the statistical analysis plan. A steep learning curve may impact labelling and training requirements for users (4.2). Further diversity of investigation sites in terms of investigator or operator experience and variation of standard of care and practice of medicine are addressed in the considerations on selection of investigation sites in section 6.6.

In the **TGA guidance**, contextual factors are mentioned only as potentially confounding factors, by citing MEDDEV 2.7/ 1 revision 4, appendix A6 [33] covering examples of studies lacking scientific validity. Under the heading "lack of adequate controls" as other influencing factors that are mentioned are user skills and the infrastructure available for planning, intervention, and aftercare. The **IMDRF guidance on clinical investigation** contains "accounting for learning curve issues" as one item to be considered in the statistical analysis [41].

4.4.7 Reporting of clinical investigations

16 documents contain guidance on the reporting of clinical investigations ([10], [12], [13], [14], [18], [19], [21], [22], [24], [26], [35], [36], [37], [40], [41], [43]).

The **FDA** provides recommendations on the contents of the study protocol and CIP [19], specific study designs ([18], [22]), and demographic subgroup analyses ([21], [24]). Two documents that were published in 2021, the **guidance on dossier content** for clinical investigations from the **Belgian Federal Agency for Medicines and Health Products** (FAMHP) [10] and the **guidance on compiling a submission for clinical investigations on medical devices from the MHRA** [13], list all items that should be reported in the CIP and the investigator's brochure. **Another MHRA document** [12] makes some recommendations about what to report in the clinical investigation report.

Four guidance documents of the MDCG ([35], [36], [37], [40]) recommend how to report clinical investigations in the "Clinical Investigation Report" submitted by manufacturers [35], in the "Summary of Safety and Clinical Performance" [40], and in the "Clinical Evaluation Assessment Report" [36] prepared by notified bodies; and how to report adverse events from the clinical investigation [37].

The **guidance document of TGA** [14] refers to ISO 14155 and to guidelines for reporting a clinical investigation. Two guidance documents from the IMDRF recommend how to report the "Clinical Investigation Plan" [41] and what terminology to use when reporting adverse events [43].

The following five tables (Tables 23–28) describe recommendations on the content of the investigator's brochure, the clinical investigation plan, the clinical investigation report, and the sections on clinical investigations in the "Summary of Safety and Clinical Performance", all of which have to be provided by the sponsor, and on the content of the clinical evaluation assessment report that has to be provided by the notified body after assessing the submission of the manufacturer.

Three jurisdictions have recommendations on the content of the investigator's brochure. In **the MDR**, its minimum content is described (see A.11). EU member states can issue additional regulations for clinical investigations and in **Belgium** there is an additional document **from FAMHP**. It and a document from **MHRA** refer to annex B of ISO 14155:2020 for the content of the investigator's brochure and add many more details about which information should be provided and in what form. ISO 14155:2020 is generally more detailed than the MDR, but the MDR is more explicit regarding the clinical data that have to be provided (see Table 24).

The **FDA, MDR, FAMHP, MHRA, and IMDRF** describe items to include in the clinical investigation plan. The FDA does so in broad terms. The FAMPH and MHRA refer to Annex A of ISO 14155 and add some recommendations for a more detailed description of methods of randomization and diagnosis, interim analyses, and study conduct. The FAHMP document gives more detailed information on risk analysis. The MHRA guidance refers to templates for reporting severe adverse events, according to MEDDEV 2.7/3 for approval in the UK or MDCG 2020-10/1 for approval in Northern Ireland. The MDR follows the items in Annex A of ISO 14155: 2020, with some small differences and fewer details especially concerning statistical considerations. The IMDRF guidance on clinical investigations lists items that should be included in the clinical investigation plan as in Table 24, without further explanations, but it provides another list of items for the statistical analysis plan (as already described in the section 4.3.7 in this report).

Table 25 shows recommendations for the content of the clinical investigation report, from TGA, MHRA, and MDCG. The IMDRF document on terminology of adverse events only considers that particular aspect. The MHRA guidance specifies only some items regarding study results. The TGA document refers to Annex D of ISO 14155:2020 and recommends using published reporting guidelines for trials specific by study type as a minimum requirement for full clinical trial reports (page 24). MDCG 2021-06 refers to the MDR, Annex D of ISO 14155:2020 as minimum requirements and to MDCG 2020-10. MDCG 2020-10 describes how to summarize severe adverse events during trials and in the clinical investigation report.

The MDR requires the manufacturer to prepare a "Summary of Safety and Clinical Performance" for implantable and class III devices. It has to be written in a way that it is clear to the intended user and, if relevant, to the patient, and made public via EUDAMED (the EU database for medical devices). A summary of the clinical evaluation must be provided, in addition to information on the medical device, manufacturer, intended purpose, indications, contraindications, target population, possible diagnostic

or therapeutic alternatives, profile of and training for users, residual risks, undesirable effects, warnings and precautions (MDR Article 32).

Table 26 is extracted from the section on clinical investigations in MDCG guidance 2019-9. MDCG 2020-13 provides a template for the clinical evaluation assessment report by the notified body:

> "A clinical evaluation assessment report (CEAR) is a report used by the notified body to clearly document the conclusions of its assessment of the clinical evidence presented by the manufacturer in the clinical evaluation report (CER) and the related clinical evaluation that was conducted – a core requirement of the Medical Device Regulation (EU) 2017/745 (MDR)." (MDCG 2020-13, page 3)

Table 27 contains the questions regarding clinical investigations that the notified body has to answer in the CEAR. The template represents the minimum content (page 4). The CEAR has to document clearly its conclusions from assessing the clinical evaluation conducted by the manufacturer (MDR, Annex VII 4. 4.5.5 and 4.6). An important component is to assess the compliance of the clinical investigation plan with the MDR and ISO 14155 Annex A, and whether the scope and design are appropriate to demonstrate the safety, performance, and benefit-risk profile of the device under consideration. The notified body has to assess if the conclusions drawn by the manufacturer on the results of its clinical investigation are valid, compared to the approved clinical investigation plan.

Table 23. Content of Investigator's Brochure in regulatory guidance documents or the MDR

MHRA	EU MDR	FAMHP
Annex B ISO 14155, additionally, more details how device description should be provided (drawings, photographs, video, for device systems etc.), identification and details of design features different from previously marketed devices, provisions for recovery of device and subsequent prevention of unauthorized use; description of new intended purpose, relevant standards that have not been applied should also be listed. Checklist of Essential requirements (ER)/ GSPR detailing how they have been addressed including references to designated or harmonized standards, evidence how standards have been met, justifications, if standards are only met in part, description of solutions how ER of UK or GSPR of MDR are met. Justification where standards have been superseded. Copies of all test reports and other documents in checklist, risk analysis preferably to ISO 14971: 2019, more detailed description how preclinical testing should be reported, if equivalence is claimed, provision of supporting data in line with MEDDEV 2.7.1, results of design calculations, confirmation of testing each device individually, for implantable devices explant and histopathological results, testing of human factors and usability engineering, more details on adverse events in clinical studies, confirmation whether devices in CI was identical to the investigational device, if not full details on differences. Sterilisation validation report requested, details of reporting provided, software information with detailed list of issues to report, detailed reporting requirements on biological safety assessment of patient contacting material, on animal tissues, medicines and blood derivatives, active devices, specialist technologies [13].	Annex XV MDR Chapter II Section 2 (see Appendix for details): Identification and description of the device, manufacturer's instructions for installation, maintenance, maintaining hygiene standards and for use; pre-clinical evaluation based on relevant pre-clinical testing and experimental data; existing clinical data, in particular: from relevant scientific literature or other relevant clinical data available; summary of the benefit-risk analysis and the risk management; for specific devices: compliance with the relevant general safety and performance requirements and the specific risk management in relation to the substance or tissues, cells or their derivatives; list detailing the fulfilment of the relevant general safety and performance requirements set out in Annex I, including the standards and CS applied; detailed description of the clinical procedures and diagnostic tests used in the course of the clinical investigation (MDR).	Annex B ISO 14155, additionally reference to MDR classification rules more detailed requirements how the information should be provided, a history of device design versions used in clinical and confirmatory preclinical trials. In summary of preclinical testing statement whether devices were identical to devices used in clinical studies, with justification, if not. Note that all pre-clinical studies have to be finished before a CI can be started, more details how animal studies should be reported, justification for study design choices, recommendation to follow the ARRIVE guideline, more detailed indications how the evaluation of biological safety, and sterilization methods should be reported. More detailed requirements for reporting of clinical existing and ongoing studies, demanding protocols, sites, and safety and performance results, ADE, SAE of each study, history of modification and recall; more detailed requirements for reporting of risk management, table of anticipated SAE and SADE, detailed information on sources for risk estimation, estimation scales used, justification for choice, inclusion of full risk analysis table, management plan and report recommended [10].

CS: common specifications, ISO: International Organization for Standardization, MEDDEV: Medical Device Directives, MDR: medical device regulation.

Table 24. Content of Clinical Investigation Plan in regulatory guidance documents or the MDR

FDA	MHRA	EU MDR	FAMHP	IMDRF
Study rationale, rational for study design regarding bias, definition of study population with inclusion criteria, intended use, study endpoints, statement of procedures, summary of analysis and evaluation methods and statistical analysis plan for data, details of sample size calculation for primary endpoint [19]. Includes additional issues for Bayesian design: prior information, success criterion, Bayesian sample size calculation, estimate of power and type I error, prior probability of study claim, effective sample size, program code [18] Additionally, description of adaptation general in protocol, detailed in SAP [22]. Additionally, identification of subgroup-specific prevalences, specification of subgroup definitions, diagnosis and treatment patterns, proportions included in past studies, clinically meaningful outcome differences, pre-specified plans for subgroup analyses ([21], [24]).	Annex A ISO 14155 more details randomization, diagnosis methods, interim analysis, conduct of study in a pandemic [13].	Annex XV MDR Chapter II Section 3 (details see Appendix) Identification of CI, sponsor, principal investigator, financing, synopsis of CI, identification and description of device; risks and benefits of device and expected clinical outcomes; relevance of CI, objectives and hypotheses; design of the CI with evidence of scientific validity; information on investigational device, comparators, other devices and medications, information on subjects; approach to bias; description of procedures and diagnostic methods, deviation from routine practice; monitoring plan; statistical considerations; data management; amendments to CIP; Follow-up policy and for deviations from CIP; accountability regarding device; compliance with ethical standards; informed consent process; safety reporting; criteria follow-up, halt or termination, withdrawal of informed consent; care for subjects after the CI; policy for CIR and publications, list of technical and functional features of the device, bibliography (MDR).	Annex A ISO 14155 additionally more details in risk description [10].	Study objectives, appropriate subject population(s), adverse event definitions and reporting, study endpoints, minimization of risk to subjects, minimization of bias, confounding factors, choice of controls, study type, type of comparison, follow-up duration and monitoring, SAP details see in text “Statistical Methods”[41].

CIP: clinical investigation plan, CIR: clinical investigation report.

Table 25. Content of Clinical Investigation Report in regulatory guidance documents or the MDR

TGA	MHRA	EU MDR	IMDRF
Annex D ISO 14155 plus study-type specific reporting guidelines: CONSORT, STROBE, STARD [14].	Reporting of all patients with exclusion reasons, measurements for all important variables at all relevant time points, information for patients not randomized, effect of loss-to follow-up, reporting of reasons, suitable tables / figures for primary and secondary variables, prognostic, and demographic variables, Additional work not prespecified should be clearly distinguished [13].	MDR Annex XIV chapter III point 7, Annex D of ISO 14155. In addition to minimum requirements: Background of CI, description of outcome measures and their relevance for safety and performance assessment. CI conduct: recruitment periods and follow-up, precise details of interventions, dose duration, control interventions, additional treatment CI subjects, baseline data, flow of subjects: numbers of subjects randomized, receiving treatment, completing CI, primary endpoint analysis, whether analysis was intention-to-treat or per protocol Description of deviations from initial CIP and amendments, reporting of adverse events according to template of MDCG 2020-10 [35] [37]. See text relating to PICO Outcomes.	Adverse Event Reporting according to terminology of IMDRF [43]. See text relating to PICO Outcomes.

CI: clinical investigation, CIP: clinical investigation plan, CONSORT = Consolidated Standards of Reporting Trials, IMDRF: International Medical Device Regulators Forum, ISO: International Organization for Standardization MDCG: Medical Device Coordination Group, MDR: Medical Device Regulation, PICO: Population Intervention Comparator Outcome, STARD: Standards for Reporting Diagnostic accuracy studies, STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

Table 26. Content of Summary of Safety and Clinical Performance, 5.2 Clinical investigations conducted before CE marking / EU MDCG 2019-9 Revision 1 (40)

EU (MDCG 2019-9)
• Identity of the investigation/study. • Identity of the device including any model number/version. • Intended use of the device in the investigation. • Objectives of the study. • Study design: randomized controlled trial, other pivotal trial, short-term feasibility study, other; and the duration of the follow-up. • Primary and secondary endpoint(s). • Inclusion/exclusion criteria for subject selection. • Number of enrolled subjects, including if applicable in different treatment arms. • Study population: main baseline characteristics of each study group, including gender and age of enrolled subjects. • Summary of study methods. • Summary of results: any clinical benefits; any undesirable side-effects or adverse events, and their frequency in relation to time; any results on long-term benefits or risks, for example implant survival rates at 5 or 10 years and/or cumulative experience in patient-years. A statement of percentage completeness of follow-up should be provided. Add a note if the study is still ongoing for long-term follow up. • Any limitations of the study, such as high loss to follow-up, or potential confounding factors that may question the results. • Any device deficiency and any device replacements related to safety and/or performance during the study.

EU: European Union, MDCG: Medical Device Coordination Group.

Table 27. Content of Clinical Evaluation Assessment Report, Section E Clinical Investigations MDCG 2020-13 (36)

EU (MDCG 2020-13)
• Has the manufacturer conducted clinical investigation(s)? State Yes / No • Has the manufacturer conducted pre-market or post-market clinical investigations? Provide detail. • If the manufacturer has not conducted clinical investigation: What is the rationale? Why is this acceptable / unacceptable? • Has the manufacturer provided a copy of all clinical investigation reports? State Yes / No • Were all clinical investigations publicly registered? State Yes / No • Have been verified that clinical investigations conducted with respect to Regulation (EU) 745/2017 publicly registered on EUDAMED? State Yes / No • Did the clinical investigations result in a publication in a scientific journal? • Has the manufacturer provided all Competent/Regulatory Authority correspondence (from all countries, including outside of EU)? State Yes / No • Are the conclusions drawn by the manufacturer, based upon the results of the clinical investigation, valid in the light of the approved clinical investigation plan? Provide detail. • If clinical investigations not performed under Regulation (EU) 745/2017 were not publicly registered or published: Confirm that a rationale was provided. • Confirm that the SSCP and where relevant the IFU (for example with respect to the description of clinical benefits) adequately provide information for the intended user and if relevant, the patient. • Clinical Investigation Plan (CIP) reference • CIP complies with MDR, Annex XV, and EN ISO 14155 Annex A State Yes / No • CIP scope and study design • Adequacy of CIP scope and study design for demonstration of safety, performance and benefit risk of subject devices: • Study design. Devices identified. Patient population. Patient numbers. Objectives and endpoints. Length of follow up and intervals. Study locations. Overall conclusions. • Non-compliances identified and resolved for this section may be briefly described. • Manufacturer clinical investigations and related documentation are: Compliant with the applicable requirements of the MDR/ Compliant with the applicable requirements of the MDR with the exception of the minor non-compliance below.

CIP: Clinical Investigation Plan, EU: European Union, EUDAMED: European database for medical devices, IFU: information for use, EN ISO: European Standard International Organization for Standardization, MDCG: Medical Device Coordination Group, SSCP: summary of safety and clinical performance.

4.4.8 Patient engagement in clinical investigations

In 2022 the FDA issued guidance on "Patient Engagement in the Design and Conduct of Medical Device Clinical Studies" that "focuses on the application of patient engagement in the design and conduct of medical device clinical studies" (III). The FDA considers that medical device clinical studies can benefit from the prospective involvement of patient advisors in study design, which could result in:

- "Faster study/research participant recruitment, enrollment, and study completion;
- Greater study/research participant commitment and retention, resulting in decreased loss to follow-up; Greater study/research participant adherence resulting in fewer protocol deviations/violations;
- Greater study/research participation by diverse patient populations;
- Fewer protocol revisions;
- Streamlined data collection resulting in better quality data; and
- More relevant data on outcomes that matter to patients."

Patient engagement is defined in the FDA guidance document as "intentional, meaningful interactions with patients that provide opportunities for mutual learning, and effective collaborations". Patients are defined as "individuals with or at risk of a specific disease or health condition, whether or not they currently receive any therapy to prevent or treat that disease/condition." Two distinct roles are identified for patients who interact with researchers, sponsors, or the FDA regarding clinical studies:

Study/research participants:

> "Study/research participants are individuals who are or become a participant in research, as a recipient of the test article, on whom or on whose specimen the test article is used, or as a control, and may include healthy individuals." [and]

Patient advisors:

> "Term patient advisors refers to individuals who have experience living with a disease or condition, and can serve in an advisory or consultative capacity to improve clinical study design and conduct, but who are not study/research participants themselves or caregivers of study/research participants." […]
>
> "To avoid potential real or perceived conflicts of interest, these patient advisors should not be study/research participants in the same study for which they are advising." (IV)

The FDA recommends that sponsors should voluntarily identify patient advisors early in the process of planning a study, clearly define their role and distinguish between activities for study participants and patient advisors. Incorporating their input into the design of a study is encouraged, especially in innovative areas. In addition, "sponsors may also want to consider involving patient advisors post-study to inform improvements for future studies" (V.B).

It is recommended to train patient advisors about clinical studies to help them to contribute most efficiently (V). Areas suggested for patient engagement "that may enhance the design and conduct of clinical studies" are:

- improvement of informed consent documents,
- input for "flexible options for follow-up visits and data collection techniques to reduce unnecessary burden on study/research participants who may have challenges fulfilling the follow-up schedule",
- to discuss barriers to recruitment or other causes for delay during an ongoing study,
- to discuss meaningful endpoints in the treatment of a disease, "to inform the concepts that should be captured by patient-reported outcome (PRO), measures in the clinical study to better reflect outcomes that are important to patients", and
- to inform the design of patient preference studies (V.A).

4.4.9 Summary and discussion

4.4.9.1 Topics addressed by guidance documents

Overall, we have included 30 guidance documents: Nineteen from national regulators in six jurisdictions [Belgium (1), UK (3), Australia (2), Canada (1), Japan (1), and the USA (11)]; 8 from the European Union [7 under the Medical Device Regulation, and 1 under the Medical Device Directives that is considered applicable in many parts under the MDR by the MDCG (38)]; and 3 from the IMDRF. Table 28 shows which topics they cover, concerning study design, analysis and reporting.

The largest single proportion (37%) comes from the **FDA**. Its central guidance from 2013, entitled "Design considerations for pivotal clinical investigations for medical devices", covers 6 of the 7 topics regarding study design, omitting only when a clinical investigation is needed. Several FDA guidance documents are dedicated to specific elements of study design and analysis or specific statistical methods – such as Bayesian statistics, adaptive designs, evaluation of data in former studies under-represented subgroups, and how patient engagement can contribute. The FDA documents also contain the most detailed recommendations and explanations.

Eight documents (27%) were issued by the **European Commission or the MDCG** in the EU. They cover 5 of 7 topics, especially reporting and the need for clinical investigations. MEDDEV 2.7/1 Rev. 4 addressed nearly all topics of general study design from the perspective of clinical evaluation, while MDCG guidance has focused on outcome issues. Levels of clinical evidence are addressed in one document on legacy devices, that does not classify study types, but considers the whole body of evidence of a clinical evaluation.

Three concise guidance documents (10%) come from the **MHRA**. Together they cover 5 of the 7 topics, excluding a hierarchy of evidence regarding study types, and context-specific factors. Three more guidance documents, that have been issued by the **IMDRF**, cover 6 of the 7 topics. The IMDRF document on clinical investigations addresses all topics except for a hierarchy of study types. Factors to consider are listed, without further details or explanations.

The detailed terminology for disease-specific reporting of adverse events that was issued in 2020 is continuously updated and used by the FDA. The guidance and templates provided by the MDCG refer only to the categorization of severe adverse events, which are applicable to all diseases.

The **TGA** document covers all topics and contains device-specific recommendations. The general section on clinical investigations is short, and its part on study design comprises only one page. Instead, it refers multiple times to guidance from the IMDRF and to MEDDEV 2.7/1 Rev. 4. For reporting, it refers to recommendations in the reporting guidelines the EQUATOR initiative. In fact, general design issues and statistical methods are touched upon only briefly; the focus is more on clinical evaluation, over 19 pages. In our analysis, we have taken some recommendations from this section, that relate to the evaluation of clinical investigations. The section on specific devices contains detailed recommendations on choice of study design and particularly on outcomes.

It is not clear to us from the information in the document of the **Japanese regulatory authority** if these are recommendations directly from the PMDA. The guidance covers 4 of 7 topics. The focus is on the 'need for a clinical investigation' and the 'choice of study design', with only brief reference to some aspects of 'general design issues' and 'statistical methods'. The document has an appendix that gives case examples when a clinical investigation was not needed, and that provides an overview of clinical investigations for medical devices in different disease fields to illustrate what sample sizes are needed.

The guidance document from **Health Canada** has a restricted theme from the outset. It covers participation of women in trials (including prevention of pregnancy) and therefore contributes to the subtopic 'study population' related to general design issues and to the subtopic 'subgroup analysis' concerning statistical methods. The recommendations on these aspects of design are concise and general.

The guidance document from the **FAMHP** in Belgium focusses only on the content that has to be included in a dossier submitted for a clinical investigation under the MDR.

In Table 28 below, we have used large and small 'x's to indicate whether a topic was covered in detail.

Table 28. Topics covered in guidance documents of national regulators

Regulatory document	Level of evidence / Study Types	Need for CI / Substantial equivalence	Choice of study design	General design, objective / PICO	Statistical methods	Context / learning curve	Reporting
FDA 2010 Bayes	-	-	X	X	X	-	X (protocol)
FDA 2013 Design Pivotal	X	-	X	X	X	X	X (protocol)
FDA 2014 510 k Subs. Equival.	(X)*	X	-	-	-	-	X
FDA 2014 Sex-specific data	-	-	-	x (P)	X	-	X
FDA 2016 Adaptive Designs	-	-	-	-	X	-	X (adaptation)
FDA 2017 Age, Race, ethnicity data /FDA 2016 collection Race	-	-	-	x (P)	X	-	X
FDA 2019a Benefit-Risk	-	-	-	X (O)	-	-	-
FDA 2019b Uncertainty in Benefit-Risk Determination	-	-	-	-	x	-	x post-market shift in SSED
FDA 2022 Health of Women	-	-	-	X (P)	x	-	-
FDA 2022 Patient Engagement	-	-	-	x	-	-	-
TGA 2022 /NHMRC Evidence requirements	X	X	X general X device-specific	x general X device-specific	x	x	X ISO 14155 and reporting stand.
MHRA 2021 compiling a submission	-	-	-	-	-	-	X CIP ISO p8f IB ISO
MHRA 2021 CI Manufact.	-	X	X	X	-	-	-
MHRA 2021 CI. Stat. Consid.	-	-	X	X	X	-	x

Regulatory document	Level of evidence / Study Types	Need for CI / Substantial equivalence	Choice of study design	General design, objective / PICO	Statistical methods	Context / learning curve	Reporting
Health Canada 2013 Women	-	-	-	x	x	-	-
FAMHP 2021 CI. Dossier content	-	-	-	-	-	-	CIP, IB, CEP
PMDA 2017 Clin. Trial guid.	-	X	X	x	x	-	-
MEDDEV Clinical Evaluation	-	X	-	X	X	-	
MDCG 2019-9 Rev. 1 SSCP	-	-	-	-	-	-	X (SSCP)
2020-6 Legacy devices	-	X	-	X	-	-	-
MDCG 2020-5 Equivalence	-	X	-	-	-	-	-
MDCG 2020-10 Safety reporting in CI	-	-	-	X	-	-	X (safety)
MDCG 2020-13 CEAR template	-	-	-	-	-	-	X
MDCG 2021-06 Q&A CI	-	-	-	x	-	-	X
MDCG 2021-08 CI application	/x	-	-	-	-	-	-
IMDRF 2019 CI	-	X	X	X	X	X	X
IMDRF 2019 Clinical Evaluation	-	-	-	-	-	-	-
IMDRF 2020 AE reporting	-	-	-	X	-	-	X (safety)

* Provided study type list with descending evidence level in Appendix.

CI: clinical investigation, CEAR: clinical evaluation assessment report, CEP: clinical evaluation plan, CIP: clinical investigation plan, FAMHP: Belgium Federal Agency for Medicines and Health Products, FDA: U.S. Food and Drug Administration, Health Canada: Health Canada Medical Devices Bureau of the Therapeutic Products Directorate, IB: investigator's brochure, IMDRF: International Medical Device Regulators Forum, MDCG: Medical Device Coordination Group, MEDDEV: Medical Device Directives, MHRA: United Kingdom Medicines & Healthcare products Regulatory Agency, PICO: Population Intervention Comparator Outcomes, PMDA: Pharmaceuticals and Medical Devices

Agency (Japan), SSCP: summary of safety and clinical performance, SSED: summary of safety and effectiveness data, Q&A: questions and answers TGA: Department of Health, Therapeutic Goods Administration (Australia), X: topic covered more extensively, x :topic covered less extensively / or rudimentarily.

4.4.9.2 *Level of evidence of study types, need for clinical investigations, and choice of study design*

Levels of Evidence. Table 29 shows the two different 'hierarchies of evidence' that we have identified for types of clinical studies, from the FDA and the TGA.

The FDA *de facto* provides a hierarchy of evidence levels that may be used for pivotal confirmatory clinical investigations. The criterion used for the classification is the minimization of bias. Study types are not clustered into evidence classes, but if one of the first two types is not used for a premarket approval or if a randomized study is completely unblinded, then a consultation is required with FDA staff to consider how the concern of bias can be addressed.

> "Whenever a sponsor believes it is not appropriate or necessary for a clinical outcome study to be well-controlled, randomized and/or blinded, the sponsor should explain why the possible biases can be ignored."[19]

The TGA did not develop its own classification; instead, it refers to a classification by the National Health and Medical Research Council (NHMRC) in Australia, that was developed for guidelines in evidence-based clinical practice. Among several versions of hierarchy relevant to different research questions, we selected the one for studies evaluating interventions. The study types are grouped into evidence classes, which are numbered. The principle of evidence-based medicine is to use the best available evidence, and the primary perspective of an evidence hierarchy in the context of systematically aggregating evidence is to assess what is already available in literature. The prerequisite for strong recommendations about interventions is the existence of studies with a high level of evidence.

It is noticeable that the study type of the 'randomized trial' in the NHMCR classification is not further differentiated (as in the FDA classification) with regard to the type of blinding and to the controls. On the other hand, pseudo-randomized studies have no place in the FDA classification and observational study types are also not included. This may be because guidance from regulators for device developers aims to recommend the most appropriate design before a study is planned, rather than to aggregate existing evidence. Pre-market approval studies are usually experimental, and the FDA considers observational studies inappropriate for this setting (7.6.3). Exceptions are mentioned in an FDA guidance document on real-world evidence [82], and in a statement from MDIC that covers statistical methods and gives examples of how such external data may be used for pre-market approval [45].

'Risk of bias' checklists are used during systematic reviews in evidence-based medicine to assess the scientific validity of a study. They usually contain the degree of blinding and type of control, which would result in a similar order of study types as in the FDA classification for randomized studies where that criterion is already explicit. The NHMCR classification does not include the single-arm study with objective performance criteria or performance goals, as a typical type of study for already established classes of implantable devices, which suggests that the hierarchy was not specifically adapted to medical devices. A classification of study designs cannot address all validity issues of clinical investigations, but we think that the FDA hierarchy better suits the regulatory need to give advice for studies for market approval.

Table 29. Comparison of hierarchy of evidence levels by FDA and NHMRC

FDA level of evidence	NHMRC level of evidence
Randomized controlled trial	**II Randomized controlled trial**
Randomized, multi-arm, "blinded" study with concurrent sham (placebo) control	
Randomized, multi-arm, "blinded" study with concurrent ("active") control	
Randomized, multi-arm, un"blinded" study with a control (control that is either active or consists of no treatment)	
Randomized, single-arm study with patient serving as own control (include designed single-arm crossover)	
	III-1 Pseudorandomized controlled trial
Studies with concurrent controls	**III-2 Comparative study with concurrent controls**
	Non-randomized, experimental studies
	Cohort study
	Case-control study
	Interrupted time series with control
Studies with non-concurrent controls	**III-3 Comparative study without concurrent control**
Single-arm study with historical control (using patient-level data)	Historical control study
Single-arm study with literature control (historical control)	Two or more single arm study (including unadjusted indirect comparisons)
	Interrupted time series without parallel control group
Non-comparative studies	**IV Case series with either post-test or pre-test/post-test outcomes**
Single-arm study with objective performance criteria	
Single-arm study with performance goals	

FDA: U. S. Food and Drug Administration, NHMCR = National Health and Medical Research Council (NHMRC) in Australia. The hierarchies have been aligned to show their concordance.

Need for a clinical investigation. Of the six guidance documents on trial design, those from the IMDRF and 4 jurisdictions – the European Union, the United Kingdom, Australia, and Japan –recommend when a new clinical trial is required (See Table 13).

All guidance documents demand a clinical evaluation of the existing evidence, to analyze if it is sufficient to confirm compliance with relevant essential requirements for safety and performance. Guidance from the MDCG (MDCG-2020-6) addresses the specific question of when it is necessary to generate additional clinical data to demonstrate conformity under the MDR for legacy devices that have already been marketed under the MDD. In this context, the guidance provides a classification of levels of evidence for clinical evaluation (see Table 12); only the first four are relevant for implantable and class III devices. Two aspects seem to have been incorporated into the hierarchy, namely the quality of data, and secondly whether the full breadth of the intended purpose (all indications for the device) has been covered or whether there are gaps in the evidence, for example for subgroups. For the question of what constitutes high-quality clinical investigations, reference is made to clinical evaluation using appropriate appraisal tools from evidence-based medicine. It cites an IMDRF report about how to use international registry data for the clinical evaluation of performance and safety.

The IMDRF guidance on clinical investigations formulates **when new studies are needed**, in general terms: when there are new questions about safety, clinical effectiveness or intended use. The TGA, MHRA and MEDDEV documents give more specific criteria for when this is likely to be the case. The TGA cites the criteria of MEDDEV 2.7/ 1 rev. 4, which are similar to those described by the MHRA:

- high-risk (implantable or class III) device,
- approval for a new purpose,
- novelty of the entire concept, or of a particular feature that might affect clinical performance or safety, [or]
- use of materials untested in humans.

MEDDEV 2.7/ 1 rev. 4 adds as another criterion, when medical alternatives with lower risk are available. The MHRA mentions a new manufacturer of a high-risk device as a reason for the need of a new clinical investigation. The PMDA provides little guidance on this topic.

If **equivalence** to an approved device can be demonstrated, a CI is not necessary. The European Union (in MDCG-2020-6) specifies as sources for clinical evaluation of the subject device and of devices for which equivalence can be demonstrated: clinical investigations, literature reviews in peer-reviewed scientific journals, and post-market data. The TGA specifies in addition “other clinical experience data (also known as Real World Data)”, and it states that data from comparable devices that are not equivalent may also be relevant.

The MHRA seeks results from all clinical investigations and relevant scientific literature that may demonstrate if an equivalent device complies with the relevant safety and performance requirements; post-market data and real-world evidence are not mentioned. The Japanese authority mentions existing clinical data and literature, but also extrapolation of results from non-clinical studies to humans; it emphasizes that it is crucial whether the consequences of differences from already

approved medical devices can be adequately tested by non-clinical studies, but it gives little concrete information on criteria that might be used.

The European Union, TGA and FDA all provide detailed guidance about how to assess (substantial) equivalence. The intended purpose or use, and technical, biological, and clinical characteristics of the new and the predicate device are compared and evaluated, to establish if the new device will result in any clinically significant differences in performance or safety. The TGA documents point out that regulators from different jurisdictions may have different definitions of possible comparator devices or data requirements.

The other guidance documents on trial design included in this review do not cover the question of when a clinical investigation is needed. That may have been determined already in relevant legislative texts such as MDR article 62.4 which states that for implantable devices and class III devices, clinical investigations shall be performed – except if the device is a modified device of an already marketed device by the same manufacturer, and the modified device can be demonstrated to be equivalent to the marketed device, and the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

Choice of study type. Six guidance documents from four countries – the USA, UK, Australia and Japan – and a document from the IMDRF make recommendations on the choice of the study type (see Table 14).

The IMDRF does not make a statement on any specific study design. In principle the regulatory authorities from the four jurisdictions judge the randomized controlled trial as the most valid study design for a pivotal confirmatory trial. They may also accept other designs, as long as concerns about validity can be addressed, but there seems to be a slightly different emphasis among regulators on the difficulty of achieving this goal.

For a pivotal pre-market approval study, the TGA demands the highest level of evidence available that demonstrates safety and performance for the intended use. For all specific devices under consideration, it recommends a randomized controlled trial in which ideally the conditions represent clinical practice in Australia.

The Japanese regulatory authority states that a confirmatory trial is conducted preferably as a randomized study, but for an already established technology it considers single-arm studies acceptable under certain conditions. The FDA asks for justification if a study is not randomized and blinded, but for mature technologies the FDA does not rule out single-arm trials with OPC, although that design is at the low end of the evidence hierarchy. The use of this study type requires discussion of the study design with FDA staff in advance, and the guidance points out that there are “currently very few validated OPCs”.

In contrast, the MHRA states that “where the endpoints can be measured objectively, e.g. from radiological examination, the majority of clinical investigations of medical devices will not require a comparative group and a single-arm study will be sufficient to demonstrate the required objectives” (page 6) [12]. It is unclear whether the difference may be due to the fact that the FDA guidance document focuses exclusively on confirmatory pivotal pre-market approval studies with novel design

or intended use that cannot prove equivalence to a predicate via the 510k pathway, whereas the MHRA document does not restrict its focus to specific development stages. Regarding pivotal/confirmatory studies the MHRA states that they "should have a control where clinically relevant and appropriate to do so" (page 14)[11] and that for studies with subjective endpoints a control group "will nearly always be necessary" (6)[12]. For all studies, lack of a control group should be justified. The MHRA guidance was published eight years later than the FDA guidance, by which time more suitable OPCs might have been developed, but it is unclear whether OPC are meant by the MHRA guidance. There seems to be a lack of commonly used terminology here. The TGA guidance document also uses another term in the device-specific sections: performance value.

A systematic and detailed discussion of advantages and disadvantages and when to use which type of control group is provided only by the FDA (see Table 14).

4.4.9.3 General design issues

This section was divided into six subtopics: study objective, study population, intervention, comparator, outcomes, and validity. Under validity in this section, we consider only the aspects of randomization and blinding. Eleven guidance documents contributed to the topic 'study population', 13 to the topic 'outcomes', six to the topic 'comparator', six to the topic 'validity', five to the topic 'intervention', and three to the topic 'study objectives' (see Table 41).

Guidance documents from the FDA and MHRA point out that the formulation of the study objective should provide the scientific rationale for the clinical investigation supporting the intended use in the target condition and supporting any claims that are made for labelling.

In terms of recommendations about the study population, much attention has been paid in North American countries to better representing and separately analyzing the results from groups of subjects who have previously been under-represented in trials. The FDA published four documents on that topic ([19], [21], [23], [24]) and Health Canada one on women in trials [15]. When planning a clinical investigation, scientific data should be reviewed to determine whether different effects are to be expected in different subgroups. If there are indications of this, consideration should be given to possible subgroup-specific stratified recruitment and randomization and to pre-specification of subgroup analyses in the protocol. Stratification should be standard when describing the study population. Health Canada requires that in pivotal trials, even if there is no prior indication of gender-specific differences for efficacy and safety, a gender-stratified analysis is always prespecified.

More detailed recommendations on general aspects of the study population are available from the FDA and MHRA. The TGA and the Japanese regulatory authority provide a few, while there are very brief recommendations from the EU in the MEDDEV document on clinical evaluation. As can be seen in Table 15, a representative study population (Items 1 & 2 in the table) is recommended in all guidance documents, and three of the five authorities advise pre-specification of clearly defined eligibility criteria. The FDA and MHRA recommend that the representativeness of patients should be considered by collecting data on covariates. But also study sites and the skills of the investigators should reflect the standard of care and practice of medicine.

A relatively large number of documents from five legislations advise on endpoints, with the FDA and MHRA providing more details. As shown in Table 18, four specify clinically meaningful endpoints that are important for the patient, and also validation of any surrogate endpoints (items 4 & 5 in the table). The more specific recommendations of FDA and MHRA can be considered as guidance to translate study objectives and intended use into relevant primary and secondary endpoints for the clinical investigation. All jurisdictions indicate that mortality, morbidity and health-related quality of life should be endpoints.

Three jurisdictions – the USA, Australia and the European Union – also specify categories of outcomes that are relevant for assessing benefits and harms (see Table 19). The TGA guidance indicates that adverse events in general are endpoints for harms, while the US and EU documents share the terminology of device-related serious and non-serious adverse events and procedure-related complications. The FDA and the MDCG appear to have started from the ISO 14155 definition of serious adverse events, while the MDR has expanded this definition to include events leading to chronic disease. The EU guidance adds categories for the determination of a causal relationship between an intervention and adverse events. The FDA uses the disease specific IMDRF terminology for adverse event reporting during post-market surveillance; we did not identify any similar guidance from other jurisdictions.

Recent TGA guidance contains recommendations on particular types of medical devices and device-specific endpoints, based on rapid reviews of systematic reviews, HTA reports, and published trials. The rapid reviews informed recommendations on safety and performance endpoints including when relevant surrogate endpoints, and on whether objective performance criteria – which the TGA calls "performance values" – are available and if their use is reasonable. The TGA tables also summarized study characteristics of published clinical investigations, to provide information on their study design and especially on sample size. We did not include device-specific guidance from the FDA and Health Canada because their documents in the medical fields that we consider in our review were outdated.

4.4.9.4 Statistical methods and contextual factors

Overall, we included 14 guidance documents from six jurisdictions in the USA, Canada, Australia, Japan, European Union, UK, and the IMDRF (see

	Uncertainty, sample size, pre-specification, validity	Subgroup analysis	Bayesian statistics	Adaptive design
FDA 2010 Bayes	-	-	2.2, 2.6-7, 4.5.-4.8, 5, 7.1	
FDA 2013 Design Pivotal Stud.	9.3-9.4, 10	For stratified subject selection see P in PICO	-	-
FDA 2014 Evaluation Sex-specific data	-	V.A (p14-16) V.B (p16-18) V.C (p18-19-20) See Appendix 1	-	-

	Uncertainty, sample size, pre-specification, validity	Subgroup analysis	Bayesian statistics	Adaptive design
FDA 2016 Adaptive Trial Designs	-		6.c	4., 9., 10.
FDA 2016 Collection Race and Ethnicity data	-	IV	-	-
FDA 2017 Evaluating and Reporting Age, Race, ethnicity data	-	V. A reference to guidance on sex-specific data See Appendix 1	-	-
FDA 2019b Uncertainty in Benefit-Risk Determination	p12 18,22 Significance level, uncertainty	-	-	-
FDA 2022 Health of Women	-	Priority 1 p13, 15	-	-
TGA 2022 Evidence requirements	SSC: 29, 32, 34 DS (81) (statistical power calculation), 86 MEDDEV ref 31/32, 33	-	-	-
MHRA 2021 CI. Statistical considerations	SSC:1.2 Uncertainty, pre-specification,2.1 MISS 2.2, 2.3	-	-	3.2
Canada 2013 Inclusion of women	-	1.5 p8, 2.2 p13f, p14, 2.6 p25	-	-
Japan 2017 Clinical Trial guidance	5. p13	-	-	-
MEDDEV 2.7/1 Rev. 4	A6 b, c, f	-	-	-
IMDRF 2019 CI	6.0 Statistical plan	-	-	-

Table 42).

Pre-specification of all elements of the study design and analysis is covered briefly by MEDDEV, MHRA and IMDRF documents, while the TGA and PMDA mention single aspects (mainly sample size). The FDA document on the design of pivotal medical device studies emphasizes the necessity for pre-specifying statistical analyses.

FDA guidance devotes much consideration to the topic of demographic subgroup analyses, in order to promote the collection, analysis and reporting of data on groups who have been under-represented in clinical trials so far. There is Health Canada guidance on the promotion of women in clinical trials, although its focus is not on statistical issues. The scientific rationale behind these initiatives – that there are many instances where treatment effects may differ between subgroups – seems to be relevant globally, but other jurisdictions do not offer specific recommendations.

FDA guidance documents on Bayesian statistical methods and adaptive designs consider these approaches to be especially relevant for evaluation of the safety and effectiveness of medical devices. Due to incremental or iterative development, previous generations of a device with minor modifications may predict the effects of the modified device, and a Bayesian approach using prior

information from former clinical investigations may be a justification for a smaller-sized or shorter-duration pivotal trial.

Even without prior information, the Bayesian approach can be used for adaptive trials, where pre-specified changes can be implemented during a trial, for example to adapt sample size or chance of randomization schemes. Potential challenges are the need for detailed planning, that extensive mathematic modelling may be used, that modelling choices have to be agreed, that special statistical expertise is necessary, and that many stakeholders are unfamiliar with Bayesian methods. Adaptive designs nonetheless have advantages that can make medical device trials more efficient. Preplanned interim analyses allow investigators to deal with uncertainty that was present during the design phase of a clinical investigation, for example when the extent of the treatment effect of the device is unclear. After interim analysis the sample size can be adapted accordingly. If not managed correctly, however, adaptive designs may introduce operational or statistical bias that may confound the interpretation.

Regarding contextual factors, the learning curve is mentioned as a potential confounding factor by the TGA and in MEDDEV and IMDRF documents. The FDA guidance devotes more detailed attention to this issue, with respect to both data collection and analysis.

4.4.9.5 Reporting of clinical investigations

Sixteen documents from five jurisdictions (USA, Australia, EU, Belgium, UK) and the IMDRF recommend how to report clinical investigations in the regulatory setting (see Table 40):

The recommendations from MHRA and FAMHP refer mainly to ISO 14155 Annex B for the content of the investigator's brochure, and to ISO 14155 Annex A for the content of the clinical investigation plan, in each case with some more details. The requirements in the relevant parts of the MDR also summarize the content listed in ISO 14155 Annex B, with more details about clinical data to be provided by the manufacturer, but they do not specify statistical details to be included in the CIP.

The IMDRF guidance contains only a list of items, without further explanation. The FDA guidance also describes the main items briefly, since it provides much detail in the related sections elsewhere in the document. In both cases, the items comprise the rationale for the study, the rationale for its design, the elements of PICO, and the statistical analysis. The FDA guidance on Bayesian statistics and adaptive study design provides information on which additional items to pre-specify in the clinical investigation plan, and the guidance on subgroup analysis made recommendations about reporting in the clinical investigation plan and in the clinical investigation report.

Recommendations on the entire clinical investigation report are made only by the MDCG and TGA, which both refer to Annex D of ISO 14155. The TGA further refers to reporting guidelines for specific types of studies, from the EQUATOR network. The MDCG guidance adds some items to those listed in ISO 14155, such as a detailed description of the intervention.

The IMDRF recommends terminology for reporting adverse events in the clinical investigation report, and the MHRA discusses which results to report and how to report them. An important template for

EU stakeholders to report clinical investigations of implantable and class III medical devices is the "Summary of Safety and Clinical Performance", which will be publicly available in EUDAMED. The items to be reported on clinical investigations that are listed in the MDCG guidance are shown in Table 26. A detailed description of how the medical device is applied, and about relevant co-treatments, is not mentioned although that is a prerequisite for assessing whether an intervention differed between clinical investigations. It would also make it easier to judge if the intervention is applicable to a specific setting.

4.4.9.6 Methods used to derive recommendations

As already explained in 4.2.2.1, there are rarely exact descriptions in the guidance documents about how and with whose involvement the recommendations were developed. There is one indication in a MEDDEV document that stakeholders were involved. More detailed information about their processes is presented in some FDA guidance documents, generally due to the socially relevant background of disadvantage or to the desired participation of special groups. A report from 2011 describes the FDA guideline development process and gives recommendations for improvement.

It seems even more important to describe how recommendations were derived for device-specific guidance, because the state of the art in the concerned medical field may have more impact on the components of trial design than on general methodological guidance. We selected only one document, issued by TGA, which includes device-specific recommendations and provides the methods for its rapid literature reviews that were used to derive endpoints or for other design characteristics. The guidance was published in 2022 but the period of the literature search ended in 2015. Such information allows other stakeholders to recognize that a new literature search might be needed to identify the current state of the art in the medical field, for example to take account of updated recommendations from academic research consortia and/or medical professional societies. Other regulators also provided guidance documents on device-specific study design issues ([29], [30], [31], [83]); we did not include them because they were outdated but we confirmed that they did not describe methodologies used to derive recommendations, other than some literature citations.

For the sake of transparency there should be a methods section in all guidance documents, to describe the process of guideline development and explain how stakeholders were involved. At least for device-specific guidance, this section should in addition contain information on information retrieval and analysis, similar to methods reported in clinical practice guidelines.

4.4.9.7 Gaps

It may be useful to compare the results of the systematic reviews on methodologies of clinical studies in the specialist fields studied by the CORE-MD consortium, with the results of this review on regulatory guidance for pivotal clinical investigations. A practice-oriented analysis may identify gaps where further regulatory guidance on study design would be helpful. Some topics can already be derived from the information available in this review.

Objective performance criteria (OPC) are important especially for well-established technologies, but it seems that different terms are used. The FDA defines an objective performance criterion as:

> "a numerical target value derived from historical data from clinical studies and/or registries and may be used by FDA for the comparison of safety or effectiveness endpoints"

and an objective performance goal as:

> "a numerical value that is considered sufficient by FDA for use as a comparison of the pivotal study results with a safety endpoint, an effectiveness endpoint, or, in a diagnostic clinical performance study, a diagnostic performance measure".

The main distinction is the manner in which these values are derived. In the FDA view, OPC that are founded on comprehensive data can be applied especially to mature technologies. Performance goals which can be a value derived from a confidence interval are applied usually to less mature technologies, for example in a situation where there is no equipoise for any control intervention. Involvement of expert stakeholders such as medical or scientific societies is considered relevant for defining both types of performance comparators.

The TGA document uses the terms "performance value" and "generalized safety and performance value", but neither is defined. In the case of joint prostheses, the performance value should be derived from specific registries that are mentioned. For other technologies, it is stated that generalized performance values cannot be used, because of the heterogeneity of device characteristics and co-therapies.

It is unclear if the following statement in the MHRA guidance can be interpreted as supporting the use of performance goals or criteria:

> "Where the endpoints can be measured objectively, e.g. from radiological examination, the majority of clinical investigations of medical devices will not require a comparative group and a single arm study design will be sufficient to demonstrate the required objectives."

Besides clarifying terminology, we think that a methodology is needed to derive performance criteria that takes into account not only the development of the medical device under consideration but also whether confounding factors may have a decisive impact on the safety and performance outcomes. Methods to adjust for confounding factors such as the development of necessary co-therapies, and varying patient characteristics, and also to resolve the uncertainty of effect estimation, have been outlined by Hatfield et al [84].

Some general guidance documents refer to the degree of maturity of a device technology, especially when they discuss the use of historical controls. For device-specific guidance on the need for a clinical investigation and the choice of a study design, it may be helpful to distinguish more clearly in recommendations between mature and well-established technologies, and devices that are not well-established. Categories of 'new' devices would include those with no clinically relevant changes in design, those with changes in design possibly influencing the benefit-risk balance, and those that use

well-established technology without clinically relevant changes in design but in a new study population.

Regarding device-specific guidance on study design, a transparent and scientific valid and standardized methodology to collect and assess the current state of science on device-specific design issues should be applied.

From the perspective of the European regulatory system under the MDR, there is too little substantive guidance on evidence standards for the design of confirmatory studies for high-risk medical devices. Regarding trial methodology the MDCG published mainly guidance on reporting templates. Guidance on what quality of data is considered sufficient for approval is only available for the special case of additional evidence needed for legacy devices that have already been approved under the Medical Device Directives (MDCG 2020-6). However, this guidance is not about the study design of individual studies, but about the clinical evaluation of all available evidence on the medical device. Further there is no guidance on choice of study design from the MDCG. On the other hand, the FDA provides extensive guidance on this topic, including specific study designs such as adaptive and Bayesian designs, as well as topics that are also relevant in Europe, such as consideration of demographic subgroups, especially those under-represented in studies, and patient involvement in study design. For some of the recommendations regarding more complex study designs that require more individualized feedback between the manufacturer and the regulatory agency reviewing the marketing application, it is unclear how this could be implemented in the European system where the notified body responsible for certification is not allowed to provide guidance to the manufacturer.

4.4.9.8 Limitations

We may not have retrieved all relevant current documents. Often the web pages were confusing, so that it was not always clear whether all available guidance documents were listed. Internet links to other guidance documents, in the documents already retrieved, were often no longer correct. Especially if organizations (such as the FDA) issue many guidance documents and also provide much information on their home pages, relevant information might have been provided in a format that we did not search for. If there was any hint that other relevant documents might be available, that we had not identified, then we tried to identify additional information by searching with “Google”.

The extraction grid of recommendations also has limitations because there are some overarching cross-cutting concepts for assessing study design issues, such as validity and uncertainty, which are considered in all individual aspects, but then also sometimes need to be addressed in a superordinate way. The assignment to topics may therefore vary and there is also a risk of taking statements out of context. For the sake of better understanding, some topics were then covered primarily in one place, even with aspects that would actually be assigned to other topics of the extraction grid (e.g. reporting of subgroup analyses under "Statistical Methods").

In order to provide a better overview of the similarities and differences between the recommendations, individual statements on each topic have been extracted and compared in tables. However, it is important to note that the scope (e.g. pivotal trials vs. trials at all stages) and purpose (e.g. submission forms, guidance on clinical evaluation, guidance on trial design) may differ. The legal

background is also often not explicitly included, but other regulations may be included in separate documents or directly in legal acts without being mentioned. In addition, heterogeneous terminology is used.

4.5 Recommendations for Clinical Investigations of Medical Devices on General Design Issues from Public-Private Research Consortia

We included four guidance documents covering general methods for trial design of MD: two from the Medical Devices Innovation Consortium ([44], [45]) and two from the Clinical Trials Transformation Initiative ([46], [47]). Three of these documents cover specific study designs ([45], [46], [47]), which will be described first, and one provides a framework for a study protocol.

4.5.1 Methods to include external data in studies for regulatory decision-making

The "External Evidence Methods (EEM) Framework" describes study designs which use data external to the study and specifies statistical methods that can be used to appropriately analyze such data. "The document catalogs different sources of external data and some of the traditional and novel statistical methods (Frequentist and Bayesian) applicable to the design and analysis of a clinical study in which external data play a role." References are made to studies that applied these methods and were then used successfully to support approval of medical devices or to modify their indications. The guidance states that:

> "regulatory decision-making regarding medical devices is based on valid scientific evidence. In many cases, such evidence needs to be derived from clinical data. Traditionally, to collect clinical data, an investigational clinical study is planned prospectively. In some circumstances, there is an interest in obtaining supplementary clinical data from alternative sources to save time, reduce cost, or otherwise alleviate the burden of data collection" (page 9).

In section 2, the term "external data" is defined as:

> "data from sources external to the traditional clinical study being planned, where the traditional clinical study being planned is referred to as the 'current study".

Historical clinical studies, clinical studies being conducted outside the United States, medical device registries, electronic health records, lab test databases, and medical administrative claims data are all given as examples. Simulated data are also mentioned, defined as:

> "generated by computer simulation on a virtual patient population using mathematical models that incorporate information on physiological systems".

Finally, medical literature which reports results of clinical studies or case series is mentioned. Regarding published studies it is pointed out that usually only summary statistics are available, but it

is sometimes possible to get patient-level data upon request. The term “external evidence” is defined as “the clinical evidence generated by appropriate analysis of external data” (page 9).

In section 3 on the generation of external evidence, it is stated that whether external evidence is suitable to support regulatory decision-making depends on the relevance and reliability of the external data. “Relevance is the extent to which the data apply to the regulatory question at hand, are amenable to sound clinical and statistical analysis, and are interpretable using informed clinical/scientific judgment” (page 10). The following factors to consider relevance are mentioned:

- generalizability to the intended target population,
- enough information on the outcomes of interest,
- availability of specific device identification, [and]
- key baseline covariates at subject level to adjust for confounders.

Reliability concerns data accrual with processes that keep errors to a minimum, resulting in adequate data quality and integrity. These elements are mentioned as methods to ensure reliability:

- implementation of defined processes,
- appropriately qualified personnel,
- appropriate training,
- a shared common data capture form,
- a common definition convention, and
- a common follow-up schedule across sites.

Quality control is considered an important component of reliability. Historical clinical studies conducted for regulatory purposes are considered to have had good quality control, because they had to comply with quality standards such as ISO 14155 or the International Council for Harmonization (ICH) recommendations for Good Clinical Practice (GCP) (although the ICH recommendations are designed for pharmaceutical trials). Guidance that is relevant to the quality control of registries is contained in recommendations of ISO 14155, the Agency for Health Care Quality, the Patient-Centered Outcomes Research Institute, or the IMDRF. However, ISO 14155 does not contain specific recommendations on the quality of registries, and the internet links provided did not lead to specific documents with recommendations, but only generally to these organizations’ homepages. For additional considerations for assessing relevance and reliability, reference was also made to the FDA guidance document “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices” [82] and to the NESTcc Data Quality Framework [85].

In Section 3.2, Frequentist and Bayesian statistical methods are listed “that can be applied when leveraging subject-level external data” (page 10). Four propensity score methods and two Bayesian statistical procedures are described. It is stated that the propensity score methods rely on the availability of subject-level external data for both clinical outcomes and baseline covariates of interest, whereas the two Bayesian methods only rely on the availability of subject-level external data for clinical outcomes (page 11). Baseline information on covariates can be incorporated for some modelling techniques. The propensity score methodology is utilized to balance baseline covariates

between the prospectively enrolled patients from the current study and the external data, or between treatment arms in a non-randomized comparative study.

The **propensity score methodology** consists of two phases: the study design phase when the clinical protocol is developed, and the phase of outcome analysis. It is recommended that the design phase should also consist of two stages:

1. In the first stage, the decision is made which external data sources to use, the sample size is estimated and the baseline covariates that should be balanced are determined, and an independent statistician (or statistical team) is identified who has no access to outcome data.
2. In the second stage, the independent statistician or statistical team implements the propensity score strategy, assesses the covariate distribution and repeats the process iteratively until an adequate balance of covariates is reached.

The statistical analysis plan for outcome analysis is finalized. When collection of outcome data is complete, the statistical outcome analysis is performed. Important elements to ensure the validity of the analyses are not to use outcome data in the design phase, and to keep outcome data concealed from those who perform the stratification of groups by propensity score analyses. The four propensity score methods are described in Table 30.

Table 30. Four statistical methods to incorporate external data into clinical studies described in the external evidence framework in section 3.2 [45]

Method	Objective regarding study design	Description
a) Propensity score method for bias reduction in non-randomized comparative studies	To reduce bias between not randomized comparative treatment arms within the premarket regulatory setting	Two staged study design development of propensity score methodology and separate outcome analysis (see text)
b) Propensity score-integrated power prior approach for incorporating external data in single-arm clinical studies	To leverage external data to augment a single-arm clinical study	A subset of patients from the external data is selected which is similar to the patients with regard to baseline covariates in the single-arm study using propensity score methodology. The selected external patients are stratified together with those in the clinical study into more homogeneous strata. The Bayesian power prior method is used to obtain stratum specific posterior distributions which finally are combined to obtain the outcome data of interest
c) Propensity score-integrated composite	To leverage external data to augment a	The propensity score methodology is used as in b) but the combination of

likelihood approach for incorporating external data in single-arm clinical studies	single-arm clinical study	strata data is performed with a composite likelihood approach
d) Propensity score-integrated composite likelihood approach for augmenting the control arm of a randomized controlled trial (RCT) by incorporating external data	To leverage external data to augment the control arm of an RCT	Propensity score methodology selects external patients in the control arm according to the covariates of patients in the RCT and stratifies them according to similar propensity scores. A likelihood function for the intervention arm and a composite likelihood function for patients from the control arm of the study and from external data is constructed with discounting the data of external subjects. The outcome variables of interest is a weighted average of maximum likelihood estimates across all strata.

In addition, two Bayesian methods are described, as bullet points e) and f).

Bayesian hierarchical modelling can be used to combine results from multiple studies. Study level and subject level are separated in the model. The posterior distribution is derived from all studies. The exchangeability of patients within studies and the exchangeability of studies is a basic assumption in these models, which enables "to borrow strength" from the other data sources. It is stated that judgement whether the assumption holds must come from clinical and engineering perspectives. It is possible to condition the exchangeability on accounting for some variables. An example given is the extrapolation from adult data to pediatric uses of medical devices: "[…] if clinical outcomes depend on an age-related covariate, the studies may be exchangeable within each given level of the covariate" (page 13).

The second method mentioned is a statistical procedure for down-weighting external data, Bayesian power priors. Down-weighting is relevant because external sources may be very large and thus "too informative" compared to the current study. The power prior is a parameter between 0 and 1 that determines the weight of the external data in the combined outcomes results. The parameter is derived by combining the likelihood of the data from the current study with the posterior obtained when all data only come from the external data. This means that the parameter decreases, i.e. loses weight, with the heterogeneity of outcome results between the current study and the external data.

Section 4 of the guidance document deals with these topics: uses of external data, potential sources of bias, outcome-free design, and the need for prospective pre-planning. It is stated that evidence derived from external data could support a wide range of regulatory decision-making "such as approval/clearance of a new device or expansion of the indications for use of devices that are already on the market" (page 14).

These examples are given for **how external data can be used** in a medical device study:

- generating hypotheses for a prospective clinical study,
- establishing performance goals or objective performance data for a single-arm study,
- augmenting a clinical study,
- constructing an interventional or control arm for a comparative study, [and]
- generating a prior for the current study.

It is stated that the statistical methodologies discussed in the guidance document mainly address how to augment a clinical study by constructing interventional or control arms for comparison. Clinical and regulatory considerations beyond statistical ones are often critical. It is mentioned that the opportunity to embed an RCT in a registry may be explored, to save cost by using the infrastructure from the registry to collect data (registry based RCT).

Possible **sources of bias** are mentioned. Temporal biases may occur when external data has been collected years ago if medical practice and technology or the definition of outcomes have changed over time. When external data from other countries are collected, bias may be caused by regional differences in factors such as the clinical equipment available within contributing facilities, levels of clinical skills, accessibility to care, standards of care, requirement for involvement of multiple specialties, and the amount of time available for an intervention. Different sources of data may vary in the intensity and rigor that were applied when monitoring outcomes, leading for example to undercounting of adverse events. Information on important baseline characteristics must be available, so that bias due to variations can be adjusted by statistical methods. Missing data must be anticipated, and ideally a plan should be developed to handle them. Much missing data makes it unlikely that bias caused by differences in covariates can be addressed successfully (pages 14-15).

Using external data for retrospective comparison with a new intervention may jeopardize the integrity of a new study, if outcome data are already available and known while the study is being designed. Therefore **an "outcome-free" design** should be adopted, that mimics a prospectively designed study by separating the design and analysis phases, such as in the two-stage methodology described in Table 30. The essential principle is that an independent statistician designs the study without having access to the prior outcome data; they should be available only after the design has been agreed with the regulatory body. This underscores the need for prospective planning to "include details such as the external data source, a discussion of the relevance and reliability of data, information whether the external data are already collected, and statistical methodology that will be used to leverage external data to make statistical inference" (page 15).

In section 5, examples are listed of past studies that have been used for regulatory decision-making at the FDA. For all examples, the link to the summary of safety and effectiveness data has been provided.

The six examples of therapeutic devices are shown in Table 31.

An additional section lists a further selection of statistical methods that have not been applied so far in regulatory decision-making, but which are potentially applicable to leverage external data. A table in the appendix gives results from a survey of industry statisticians on their use of external data in

clinical studies, with four examples that were used for approval and nine examples that had not yet been submitted.

Table 31. Examples for use of external data in regulatory decision making at the FDA, from [45]

Link to Summary of safety and effectiveness data	Type of device	Device approval	Use of external data	External data source	Statistical method
https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047B.pdf	Ventricular assist system	First generation device approval	To construct a control arm for a prospective, non-randomized, concurrently controlled, open-label study	Patient registry for mechanically assisted circulatory support devices	Propensity score stratification with prespecified baseline covariates to test primary endpoint hypothesis in terms of difference in success rate (non-inferiority study)
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010b.pdf	Transcatheter heart valve	Indication expansion	To construct a control arm for a single-arm study	Historical clinical study	Propensity score analysis was implemented to balance baseline covariates
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010S015B.pdf	Coated balloon catheter	Indication expansion	To construct intervention and control arm in a non-randomized retrospective comparison	Historical clinical study and patient registry	Propensity score analysis was implemented to adjust for differences in baseline covariates
https://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015S128b.pdf	Drug-eluting stent	Indication expansion	To form the entire investigational device arm	4 historical clinical studies and patient registry	Bayesian hierarchical model with 4 historical studies as prior information and two patient registries as current data
https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s207b.pdf	Vagus nerve stimulation therapy device	Indication expansion	To form the entire investigational device arm	5 historical clinical studies and patient registry	Bayesian hierarchical model with 3 historical studies and a registry as prior information and a Japanese post-market study as current data
https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170030B.pdf	Drug-eluting stent	First generation device approval	To augment both investigational device and control arms of an RCT	Historical clinical studies	Bayesian hierarchical model two historical RCTs were combined with the current RCT

4.5.2 Suitability of registries for registry-based clinical trials

Recommendations from the CTTI on the suitability of registries for conducting registry-based randomized clinical trials were published in 2021 by Mikita et al [46]. Details of the CTTI Registry Trials Project had been published first in 2017 on their homepage, without a description of its methods [47]. The summary below uses information from the article, while the appendix reproduces decision trees and tables from the homepage.

"The primary goal of the project was to identify and describe the essential characteristics, practices, and processes required to embed and conduct registry-based clinical trials to support regulatory decision-making" (page 7). The scope of the project was not restricted to medical device studies, but also comprised the conduct of trials for drugs, biologics and procedures.

It is stated that "registry-embedded clinical trials offer opportunities to identify highly qualified sites, reduce duplicative data collection and site workload, identify and recruit patients more efficiently, reduce patients lost to follow-up, decrease time to database lock, accelerate time to regulatory decision-making, and reduce clinical trial costs."

The recommendations are intended to help investigators either:

1. determine if an existing registry is suitable for conducting an embedded clinical trial, or
2. design a new registry with the intention of embedding clinical trials within the registry" (page 7).

Recommendations for existing registries and new registries are shown in separate decision trees and tables (See A.12).

For existing registries, two assessments tool are provided. The first assesses "whether the historical evidence generated by an existing registry has demonstrated the relevancy, robustness, and reliability necessary to provide a platform for collecting data in an embedded clinical trial to support regulatory decision-making, with assurance of patient protections", whereas the second tool assesses "if an existing registry contains the elements needed to support a randomized clinical trial" (page 8).

The historical assessment contains three domains whose assessment criteria have to be fulfilled. To support regulatory decision-making, the registry must demonstrate relevance, robustness and reliability:

1. Questions on **relevance** comprise whether the registry is appropriate for the condition and its treatments, if the endpoints measured are relevant outcomes for the intended use, and if the evidence derived from the analysis of existing registry data are sufficient to allow clinical or regulatory decisions based on sound clinical judgement.
2. **Robustness** means whether there is sufficient evidence for the medical community to accept the registry. Indicators are high rates of participation by patients and sites, and if data from the registry are used for benchmarking, setting practice guidelines, peer-reviewed publications, or comparative effectiveness research.

3. To fulfil the **reliability** criteria, the registry should be designed to capture data from real-world practice and not protocol-driven treatment. Patients in the registry should be limited to those with specific diseases, conditions, or treatment exposure(s), and data collection forms should be standardized. It should be possible to map data elements to industry standards, to allow for more direct comparisons between analyses. The timing of each endpoint/outcome should be documented in the data collection form, and it should be possible to enter data at any time. Data should be complete, accurate and attributable.

The registry also has to assure that patient privacy is protected (see Table 1 in A.12).

Conditions are proposed to assess whether an existing registry is suitable as the basis for conducting a clinical trial:

1. it must fulfill the criteria from the historical assessment,
2. it must be assured that processes can be integrated into the registry for the assignment of treatment to eligible participants,
3. the data elements that are collected must be able to generate the data needed to answer the research questions,
4. it can be assured that appropriate data and analysis tools are available (pre-specified endpoints and statistical analysis plan),
5. there should be criteria for the reliability of the data, and adequate procedures for assuring its quality,
6. processes are established for accountability of study subjects, access for independent assessors to key data elements, and further data availability to the sponsor,
7. clinical investigators must be established,
8. privacy and data confidentiality should be maintained for patients while making appropriate data available for regulators, [and]
9. if necessary, associations to other data sources (e.g. electronic health records) should be established, with a plan for sharing data.

An additional option when assessing historical evidence is to use a device registry that lacks some necessary outcomes either for safety or effectiveness, as long as post-market data collection can provide the missing evidence. A similar option is shown for regulatory studies using existing device registries, in an additional decision tree. When a registry allows an adequate evaluation of the safety but not of the effectiveness of a device for which there is an unmet clinical need in a high-risk population, it could still be suitable if post-market evaluation will provide the additional evidence needed to establish effectiveness.

Seven requirements are listed for the design of new registries with the capability of embedding clinical trials (see Table 3 in A.12). Most of them cover processes for collecting data, using informatics standards, assuring data quality across multiple dimensions, and protecting patients.

The most relevant items for ensuring an appropriate registry study design are the identification of eligible patients, selection of clinically relevant data elements, and design of the registry for analyses by multiple stakeholders. Regarding patients' characteristics it is stated that "the registry must minimize barriers for inclusion, thus maximizing inclusion of those having the disease/condition to be

studied". Disease-specific registries are preferred to treatment-specific ones: "the registry must allow for disparate treatment modalities, including drugs, biologics, devices, and combination products".

Data elements should provide evidence on meaningful clinical endpoints, defined using recognized standards and nomenclature. The registry should have guaranteed ability to document informed consent, to undertake randomization and assignment of patients, and to configure additional data elements. It should be possible to accept external data not collected in the registry, to measure product performance, and to document adjudication or core lab determinations for key trial outcomes. The incorporation of patient-reported information within the registry is required. There are guidelines for participants about reporting to the registry, and about technologies and structures that can support periodic systematic queries.

The article describes how the recommendations were developed. A multi-stakeholder project team was composed of members of academia, the pharmaceutical and device industries, government agencies, patient representatives and patient advocacy organizations. A review of published registry trials was performed, and conclusions were drawn from commentaries, interviews with subject matter experts, and the output of a multi-stakeholder meeting (page 7).

4.5.3 National Evaluation System for health Technology Coordinating Center (NESTcc) Methods Framework

The report of the "National Evaluation System for health Technology Coordinating Center (NESTcc) Methods Framework" [44], an initiative of the Medical Devices Innovation Consortium in the USA, defines 12 key components of a study protocol for randomized and observational medical device studies, that are applicable to different data sources. The intention was "to provide guidelines on what is required to conduct a scientifically valid medical device study" (page 6). The key components are:

- Background including an understanding of the disease, available therapies, and device risk
- Description of the device
- Study-specific objectives
- Target population and patient selection
- Outcomes: primary, secondary, procedural, and device
- Device exposure and outcome schedules
- Study design including comparison treatments/devices, blinding, and control of confounders
- Study procedures
- Required sample size
- Study registration
- Monitoring plans
- Statistical analysis plan

A template is provided and its recommendations for the content of each item are considered as a minimum requirement for any study. Each component chapter is subdivided into "General principles to follow", listing sub-items and how to select and describe them, followed by a section with supporting literature, and illustrated by examples in boxes.

5 Summary and Conclusions

5.1 Summary of recommendations from regulatory guidance

The recommendations provided in the regulatory guidance documents fell into eight broad topics (Table 28, Table 40,Table 41,Table 42). These are discussed in detail throughout this report as follows:

Definition and classification of study types, levels of evidence *(section 4.4.1)*. Two documents, from the FDA in 2013 (Table 10) and from Australia in 2022 (Table 11), provide a classification and hierarchy of study designs that can be used, each of which is headed by a randomized controlled trial (see 4.4.1; and Table 29). The FDA guidance differentiates additionally the type of blinding and intends to advise study designs for market approval, whereas the TGA classification was developed in the context of clinical evaluation.

Need for a clinical investigation *(section 4.4.2,* Table 13*).* Six documents from four legislations and from the IMDRF recommend when a new clinical trial is required. All guidance documents demand a clinical evaluation of the existing evidence, to analyze if it is sufficient to confirm compliance with relevant essential requirements for safety and performance. New questions of safety, clinical performance and effectiveness and intended use are stated as general criteria for the need of a clinical trial. Some documents specify more concrete criteria. If equivalence to an approved device can be demonstrated, a clinical investigation is not necessary. Five documents contain recommendations for when devices can be considered equivalent. Criteria to consider are similar in most of the included documents, but what is accepted as predicate device differs.

Choice of study design for pivotal clinical investigations *(section 4.4.3,* Table 14*).* Six documents from four countries and the IMDRF make recommendations on the choice of study type. The IMDRF does not make a statement on any specific study design. In principle the regulatory authorities from the four jurisdictions judge the randomized controlled trial as the most valid study design for a pivotal confirmatory trial. They may also accept other designs, as long as concerns about validity can be addressed, but there seems to be a slightly different emphasis among regulators on the difficulty of achieving this goal. Some criteria are mentioned in all documents. A systematic and detailed discussion of advantages and disadvantages and when to use which type of control group is provided only by the FDA.

General design issues, investigation objective, and Population-Intervention-Population-Outcomes (PICO) *(section 4.4.4).* Two documents point out that the formulation of the study objective should provide the scientific rationale for the clinical investigation supporting the intended use in the target condition and supporting any claims that are made for labelling.

Eleven documents make recommendations about the study population. All of them state that the subjects in a trial should be representative of the target population, and three of the five authorities advise pre-specification of clearly defined eligibility criteria (Table 15). Much attention has been paid in North American countries to better representing and separately analyzing the results from groups of subjects who have previously been under-represented in trials. The FDA published four documents on that topic and Health Canada one on women in trials.

Six guidance documents contain recommendations on intervention or medical devices. Four provide detailed lists with items to describe.

Six documents give recommendations on comparators that are considered appropriate in a clinical investigation of medical devices. The most extensive guidance on study controls comes from the FDA.

Twelve documents from five legislations advise how to select endpoints and outcomes for device trials (see 4.4.4, and Table 18) with the FDA and MHRA providing more details. As shown in Table 18, four specify clinically meaningful endpoints that are important for the patient, and also validation of any surrogate endpoints.

Statistical methods *(section 4.4.5).* Fourteen guidance documents from six jurisdictions were included. Seven of them were issued from the FDA and five of them focused on specific methods such as Bayesian design or adaptive trials, and subgroup analysis in order to promote the collection, analysis and reporting of data on groups who have been under-represented in clinical trials so far. Pre-specification of all elements of the study design and analysis is demanded in most jurisdictions and the IMDRF.

Contextual factors and learning curve *(section 4.4.6).* Contextual factors and the learning curve are mentioned as a potential confounding factor by the TGA and in MEDDEV and IMDRF documents. The FDA guidance devotes more detailed attention to this issue, with respect to both data collection and analysis.

Reporting of clinical investigations *(section 4.4.7).* Sixteen documents from five jurisdictions (USA, Australia, EU, Belgium, UK) and the IMDRF recommend how to report clinical investigations in the regulatory setting. Relevant documents in all jurisdictions are the investigator's brochure (Table 23) considered in three documents, the clinical investigation plan, i. e. the study protocol (Table 24) considered in five guidance documents, and the clinical investigation report considered in four documents (Table 25).

All guidance on the investigator's brochure refer to Annex B of ISO 14155 as minimum requirement with some complements. Recommendations on the entire clinical investigation report are made only by the MDCG and TGA, which both refer to Annex D of ISO 14155. The TGA further refers to reporting guidelines for specific types of studies, from the EQUATOR network. The MDCG guidance adds some items to those listed in ISO 14155, such as a detailed description of the intervention. An important template for EU stakeholders to report clinical investigations of implantable and class III medical devices is the "Summary of Safety and Clinical Performance", which will be publicly available in EUDAMED. The items to be reported on clinical investigations that are listed in the MDCG guidance are shown in Table 26. A further template represents the minimum content of the clinical evaluation assessment report, which is used by notified bodies to document their conclusions of its assessment of clinical evidence (Table 27). Reporting of adverse events in a trial and the clinical investigation report is also subject of a MDCG guidance document.

Patient engagement in clinical investigations *(section 4.4.8).* In 2022 the FDA issued guidance on "Patient Engagement in the Design and Conduct of Medical Device Clinical Studies" that focuses on the application of patient engagement in the design and conduct of medical device clinical studies.

Areas suggested for patient engagement are the improvement of informed consent documents, input on barriers to recruitment unnecessary burden on study participants for data collection, discuss meaningful endpoints, informing the design of patient preference studies.

Methods used to derive recommendations

There are rarely exact descriptions in the guidance documents about how and with whose involvement the recommendations were developed. There is one indication in a MEDDEV document that stakeholders were involved. More details about their processes are presented in some FDA documents, generally due to the socially relevant background of disadvantage or to the desired participation of special groups. A report from 2011 describes the FDA guideline development process and gives recommendations for improvement.

The section on device-specific recommendations in the document issued by the TGA provides the methods for its rapid literature reviews that were used to derive endpoints or for other design characteristics. The guidance was published in 2022, the period of the literature search ended in 2015.

5.2 Summary of guidance from ISO standards and Regulatory-Private Academic Research Consortia

The general standard ISO 14155 on good clinical practice for clinical investigations of medical devices covers non-IVD devices of all risk classes (section 4.3) It does not establish a hierarchy of levels of evidence related to study designs for performing clinical investigations. The definition of design types used in ISO 14155, as “exploratory, confirmatory or observational”, is neutral with respect to level of evidence. A confirmatory study is an "adequately controlled" intervention study with pre-specified hypotheses for the primary endpoint(s) and the correct confirmatory statistical tests. Recommendations are very general and rarely study type specific. It includes annexes with reporting structures of the study protocol, the study report, and the "Investigator's Brochure". Regulatory guidance often refers to these annexes as minimum standards.

We included four ISO standards on implants for heart valves, and five on other cardiovascular implants. A detailed comparison of recommendations regarding the topics specified above is shown in Table 9.

All standards recommend a clinical investigation for all new devices or for expanded use of a device. Five standards (heart valves & standard on cardiovascular absorbable implants) recommend a randomized clinical trial for the clinical investigation of a new device, whereas the other four standards on cardiovascular implants recommend multi-center trials with a control group, or else a justification for no control group. ISO 5840-2 (heart valves) recommends incorporating objective performance criteria in the study design for established devices.

Regarding general design issues, the PICO specifications are especially relevant for device-specific recommendations. The degree of detail and elaboration of recommendations is different for the four elements and between standards. The standards for heart valves are all structured according to the same scheme, as are the standards for cardiovascular implants but using a different structure. The standards on heart valves give more detailed recommendations on study population, control group,

statistical methods, whereas the other standards often use only general terms or refer to ISO 14155. But all standards provide detailed recommendations for primary and secondary safety and effectiveness endpoints.

Two reports from the Medical Device Innovation Consortium (MDIC), and a report and a journal article from the Clinical Trials Transformation Initiative (CTTI) which resulted from the same project are included (section 4.5).

MDIC provides guidance on statistical methods to include external data in studies for regulatory decision making. References are made to studies that applied these methods and were then used successfully to support approval of medical devices or to modify their indications. In principle single arm studies are augmented by external data. Whether these methods are acceptable for approval depends on the relevance and reliability of the data.

The second publication defines twelve key components of a study protocol for randomized and observational medical device studies, that are applicable to different data sources. A template gives details of the content of these components. The intention was “to provide guidelines on what is required to conduct a scientifically valid medical device study”.

The CTTI developed recommendations how the suitability of registries for conducting registry-based randomized clinical trials can be assessed. The scope of the project was not restricted to medical device studies, but also comprised the conduct of trials for drugs, biologics, and procedures. Three central criteria are relevance, robustness and reliability of a registry.

Methods used to derive recommendations

There is no information in the general or device-specific ISO standards about the methods that have been used to develop recommendations. Thus, it is unclear how the current state of science in the field has been collected and taken into account. If the bibliography can be considered as an indicator which information was used, then taking into account of recommendations from the relevant academic research consortia of clinical experts seems to be an exception.

The methodology used to derive recommendations was described for MDIC and CTTI (see section 4.2.3.1).

5.3 Gaps

Objective Performance Criteria can be used as comparator for well-established devices. There seems to be no common terminology across regulators. Besides clarifying terminology, methodology is needed to derive and update performance criteria that considers confounding factors which may have a decisive impact on the safety and performance of a device. For device-specific guidance, it may be helpful to distinguish more clearly between mature and well-established technologies.

It may be useful to compare results from the CORE-MD systematic reviews on methodologies of clinical studies, with regulatory guidance for pivotal clinical investigations. A practice-oriented analysis may identify gaps where further regulatory guidance on study design would be helpful.

To identify research gaps in the study design of confirmatory studies relevant to practice, the experience of the notified bodies and expert panels providing an opinion on the evidence in the clinical evaluation assessment report could also be drawn upon.

From the perspective of the European regulatory system under the MDR, there is too little substantive guidance on evidence standards for the design of confirmatory studies for high-risk medical devices. Regarding trial methodology the MDCG published mainly guidance on reporting templates. Guidance on what quality of data is considered sufficient for approval is only available for the special case of additional evidence needed for legacy devices that have already been approved under the Medical Device Directives (MDCG 2020-6). However, this guidance is not about the study design of individual studies, but about the clinical evaluation of all available evidence on the medical device. Further there is no guidance on choice of study design from the MDCG. On the other hand, the FDA provides extensive guidance on this topic, including specific study designs such as adaptive and Bayesian designs, as well as topics that are also relevant in Europe, such as consideration of demographic subgroups, especially those under-represented in studies, and patient involvement in study design. For some of the recommendations regarding more complex study designs that require more individualized feedback between the manufacturer and the regulatory agency reviewing the marketing application, it is unclear how this could be implemented in the European system where the notified body responsible for certification is not allowed to provide guidance to the manufacturer.

5.4 Limitations

We may not have retrieved all relevant current documents from regulatory websites and ISO standards, although we have traced all the cross-references to other possibly relevant documents as well.

In order to provide a better overview of the similarities and differences between the recommendations, individual statements on each topic have been extracted and compared in tables. However, it is important to note that the scope (e.g. pivotal trials vs. trials at all stages) and purpose (e.g. submission forms, guidance on clinical evaluation, guidance on trial design) may differ. The legal background is also often not explicitly included, but other regulations may be included in separate documents or directly in legal acts without being mentioned. In addition, heterogeneous terminology is used.

5.5 Conclusions

There is detailed and systematic guidance on study design of high-risk medical devices from regulators available regarding level of evidence, need for a clinical investigation, choice of study design, general design issues and PICO, and statistical methods, but this guidance comes mainly from the FDA. Guidance from MDCG so far is predominantly limited to reporting templates, only the MEDDEV 2.7/1. revision 4 guidance document still issued under the Medical Device Directives contains more substance matter guidance on trials design, but from the viewpoint of clinical evaluation. For a better predictability what is considered appropriate study design under the MDR development of guidance for trial design by the MDCG is still needed.

For device-specific guidance on study design, whether from regulators or the International Organization for Standardization, a transparent, scientifically valid, and standardized methodology should be applied to collect and assess the current state of science on device-specific design issues.

To identify practically relevant research gaps in the study design of confirmatory studies, the experience of the notified bodies and expert panels providing an opinion on the evidence in the clinical evaluation assessment reports should be used.

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Appendices

A.1 Searched Websites

Table 32: Websites of relevant institutions for identification of recommendations on trial design

Organization	URL
International standardization and medical device regulatory organizations	
International Organization for Standardization (ISO)	www.iso.org
International Medical Device Regulators Forum	www.imdrf.org/documents
European Commission	https://ec.europa.eu/health/md_sector/new_regulations/guidance_en https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_guidance_meddevs.pdf
National regulators	
Austria Federal Ministry of Health BASG - Austrian Federal Office for Safety in Health Care Surveillance / AGES – Austrian Medicines & Medical Devices Agency	https://www.basg.gv.at/gesundheitsberufe/klinische-studien/klinische-pruefung-medizinprodukte
Belgium Federal agency for medicines and health products (FAMPH)	https://www.famhp.be/en/human_use/health_products/medical_devices_accessories/clinical_evaluation/DM_AIMD
Bulgarian Drug Agency	https://www.bda.bg/en/administrative-services
Croatia Agency for Medicinal Products and Medical Devices	https://www.halmed.hr/en/Medicinski-proizvodi/
Cyprus Medical Devices Competent authority	https://www.moh.gov.cy/moh/mphs/mphs.nsf/page21_em/page21_em?OpenDocument
Ministry of Health of the Czech Republic Dep.of Pharmacy	https://www.mzcr.cz/en/the-ministry-of-health/
Danish Medicines Agency	https://laegemiddelstyrelsen.dk/en/devices/

Organization	URL
Estonia Health Board Medical Devices Department	https://www.terviseamet.ee/en/medical-devices
Finland National supervisory Authority for Welfare and Health, Valvira	https://www.valvira.fi/web/en/valvira/about-this-site
Agence nationale de sécurité du médicament et des produits de santé (ANSM) Ministère des solidarités et de la santé (DGS)	https://ansm.sante.fr/documents/reference/reglementation-relative-aux-essais-ou-investigations-cliniques/reglementation-des-dm-et-dmdiv-relative-aux-recherches-impliquant-la-personne-humaine https://drees.solidarites-sante.gouv.fr/
Germany Federal Ministry of Health: Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG) Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)	https://www.zlg.de/medizinprodukte https://www.bfarm.de/DE/Medizinprodukte/_node.html
Greece National Organization for Medicines (EOF)	https://www.eof.gr/web/guest/medicaldevices
Hungary National Institute of Pharmacy and Nutrition	https://ogyei.gov.hu/about_us
Ireland Health Product Regulatory Authority (HPRA)	https://www.hpra.ie/homepage/medical-devices
Italy Ministry of Health	https://www.salute.gov.it/portale/temi/p2_3_dispositivi.html
Latvia Ministry of Health	https://www.vm.gov.lv/lv
Lithuania State Health Care Accreditation Agency under the Ministry of Health	https://vaspvt.gov.lt/en
Luxembourg Ministère de la Santé	https://sante.public.lu/fr/index.php
Malta Competition and Consumer Affairs Authority	https://mccaa.org.mt/
Netherlands Health & Youth Care Inspectorate	https://english.igj.nl/medical-technology

Organization	URL
Ministry of Health, Welfare & Sports	https://www.government.nl/ministries/ministry-of-health-welfare-and-sport
Poland The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	http://www.urpl.gov.pl/en/medical-devices
Portugal National Authority of Medicines and Health Products, IP. (INFARMED)	https://www.infarmed.pt/web/infarmed-en/medical-devices
Romania National Agency for Medicines and Medical Devices	https://www.anm.ro/en/dispozitive-medicale/
Slovakia State Institute for drug control (Medical Devices Section)	https://www.sukl.eu/medical-devices/clinical-evaluation-of-medical-devices
Spain Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS)	https://www.aemps.gob.es/productos-sanitarios/productossanitarios_prodsanitarios/
Sweden Medical Products Agency	https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/clinical-investigation-of-medical-devices#hmainbody1
Norway Directorate of Health - Norway	https://legemiddelverket.no/english/medical-devices/regulatory-information-regarding-medical-devices/clinical-investigation-of-medical-devices
United Kingdom Medicines & Healthcare products Regulatory Agency	https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety
Switzerland Swiss medic, Swiss Agency for Therapeutic Products	https://www.swissmedic.ch/swissmedic/en/home/medical-devices/klinische-versuche/bewilligungsverfahren.html
United States of America	www.fda.gov

Organization	URL
U.S. Food and Drug Administration	
Canada Health Canada	https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices.html
Australia Department of Health, Therapeutic Goods Administration	https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd
Japan Ministry of Health, Labor and Welfare	https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/index.html
Regulatory-academic or private research consortia	
Clinical Trial Transformation Initiative	www.ctti-clinicaltrials.org
Medical Device Innovation Consortium	https://mdic.org/resource-library/
Regulatory Horizons Council, United Kingdom	https://www.gov.uk/government/groups/regulatory-horizons-council-rhc

A.2 Search and Selection of ISO standards

We used the list of ISO 16142-1: 2016 “Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards” with 129 ISO standards as starting point to select possible relevant ISO standards for high-risk implantable medical devices (classes IIb and III) up to 2016 which contained a chapter on clinical investigation in the preview function (see Table 34).

We excluded ISO standards either not dealing with a high-risk implant or contained no chapter on clinical investigation or evaluation. Pertaining to device-specific ISO standards we excluded all standards of devices from other fields than cardiology, orthopaedics, or diabetics.

ISO 16142-1 was published in 2016. To check whether new relevant ISO standards were published in 2016 and later, we searched the online browsing platform of ISO searching for all standards with the term “medical device”. We performed the search on May 18, 2021. We found 1668 hits and using the selector “technical sector” “Health, medicine and laboratory equipment” this was reduced to 860 hits. Of these 860 hits, we used the selector “publication year” and checked only the hits for the years from 2016 to 2021 (75, 75, 87, 87, 80, 47 hits respectively) in detail. Among these 451 hits, we found 6 further ISO standards containing a chapter on clinical investigation or evaluation in the preview function of the Table of Contents (see Table 34).

Further, we searched for ISO standards with the term “clinical investigation” without time restriction providing 109 hits. After checking in the preview function at the ISO website, we found four further ISO standards containing “clinical investigation” in title or a chapter on clinical investigation in the preview function on table of contents (see Table 35).

We included 13 ISO standards (5840-1, 5840-2, 5840-3, 5841-2, 7198, 14155 14602, 14607, 14630, 14971, 24971, 25539-1, 25539-2) from Table 33, and 4 ISO standards (5910, 12417-2, 14283, 17137) from Table 34, for a check of relevance in the full texts of ISO standard documents (see Table 36). A reviewer of Team-NB (RH) and a second reviewer (PSI) checked the full-text ISO documents, whether the ISO standards in Table 36 contained relevant details on trial design in the chapters on clinical investigation or evaluation. For 11 ISO standards this was the case. Another ISO standard 12417-1: 2021 “Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products Part 1: General requirements was identified as reference in the ISO 17137. It is a published draft version.

Finally, we included 12 ISO standards for data extraction, which are listed in Table 3.

Table 33. List of 129 ISO standards for medical devices in ISO16142 (2016): General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards

ISO standard	Exclusion reason, inclusion/check
ISO 1135 (all parts), Transfusion equipment for medical use	No implant
ISO 3107, Dentistry — Zinc oxide/eugenol cements and zinc oxide/non-eugenol cements	No implant
ISO 3826 (all parts), Plastics collapsible containers for human blood and blood components	No implant
ISO 5356 (all parts), Anaesthetic and respiratory equipment — Conical connectors	No implant
ISO 5359, Anaesthetic and respiratory equipment — Low-pressure hose assemblies for use with medical gases	No implant
ISO 5360, Anaesthetic vaporizers — Agent-specific filling systems	No implant
ISO 5361:[1], Anaesthetic and respiratory equipment — Tracheal tubes and connectors	No implant
ISO 5362, Anaesthetic reservoir bags	No implant
ISO 5364, Anaesthetic and respiratory equipment — Oropharyngeal airways	No implant
ISO 5366 (all parts), Anaesthetic and respiratory equipment — Tracheostomy tubes	No implant
ISO 5367, Anaesthetic and respiratory equipment — Breathing sets and connectors	No implant
ISO 5832 (all parts), Implants for surgery — Metallic materials	No CIC
ISO 5834 (all parts), Implants for surgery — Ultra-high-molecular-weight polyethylene	No CIC
ISO 5838 (all parts), Implants for surgery — Metallic skeletal pins and wires	No CIC
ISO 5840-1:2021(en) Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements	Check
ISO 5840-2:2021(en) Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes	Check
ISO 5840-3:2021(en) Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques	Check

ISO standard	Exclusion reason, inclusion/check
ISO 5841 (all parts), Implants for surgery — Cardiac pacemakers Part 2: Reporting of clinical performance of populations of pulse generators or leads	Check
ISO 6474-1, Implants for surgery — Ceramic materials — Part 1: Ceramic materials based on high purity alumina	No CIC
ISO 7000, Graphical symbols for use on equipment — Registered symbols	No CIC
ISO 7010, Graphical symbols — Safety colours and safety signs — Registered safety signs	No CIC
ISO 7153-1, Surgical instruments — Metallic materials — Part 1: Stainless steel	No CIC
ISO 7197, Neurosurgical implants — Sterile, single-use hydrocephalus shunts and components	No CIC
ISO 7198, Cardiovascular implants — Tubular vascular prostheses	Check clause 10.1 on clinical investigation
ISO 7199, Cardiovascular implants and artificial organs — Blood-gas exchangers (oxygenators)	No complete implant
ISO 7206 (all parts), Implants for surgery — Partial and total hip joint prostheses	No CIC (technical testing)
ISO 7207 (all000 parts), Implants for surgery — Components for partial and total knee joint prostheses	No CIC (technical testing)
ISO 7376, Anaesthetic and respiratory equipment — Laryngoscopes for tracheal intubation	No implant
ISO 7396 (all parts), Medical gas pipeline systems	No implant
ISO 7405, Dentistry — Evaluation of biocompatibility of medical devices used in dentistry	No CIC
ISO 7494 (all parts), Dentistry — Dental units	No CIC
ISO 7864, Sterile hypodermic needles for single use	No implant
ISO 7886 (all parts), Sterile hypodermic syringes for single use	No implant
ISO 8185, Respiratory tract humidifiers for medical use — Particular requirements for respiratory humidification systems	No implant
ISO 8536 (all parts), Infusion equipment for medical use	No implant

ISO standard	Exclusion reason, inclusion/check
ISO 8537, Sterile single-use syringes, with or without needle, for insulin	No implant
ISO 8637, Cardiovascular implants and extracorporeal systems — Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators	No complete implant
ISO 8638, Cardiovascular implants and extracorporeal systems — Extracorporeal blood circuit for haemodialysers, haemodiafilters and haemofilters	No complete implant
ISO 8827, Implants for surgery — Staples with parallel legs for orthopaedic use — General requirements	No complete implant
ISO 8828, Implants for surgery — Guidance on care and handling of orthopaedic implants	No CIC
ISO 8835-7, Inhalational anaesthesia systems — Part 7: Anaesthetic systems for use in areas with limited logistical supplies of electricity and anaesthetic gases	No implant
ISO 9168, Dentistry — Hose connectors for air driven dental handpieces	No implant
ISO 9170 (all parts), Terminal units for medical gas pipeline systems	No implant
ISO 9360 (all parts), Anaesthetic and respiratory equipment — Heat and moisture exchangers (HMEs) for humidifying respired gas in humans	No implant
ISO 9583, Implants for surgery — Non-destructive testing — Liquid penetrant inspection of metallic surgical implants	No CIC
ISO 9584, Implants for surgery — Non-destructive testing — Radiographic examination of cast metallic surgical implants	No CIC
ISO 9626, Stainless steel needle tubing for the manufacturer of medical devices	No implant
ISO 9713, Neurosurgical implants — Self-closing intracranial aneurysm clips	No complete implant
ISO 10079 (all parts), Medical suction equipment	No implant
ISO 10524 (all parts), Pressure regulators for use with medical gases	No implant
ISO 10555 (all parts), Intravascular catheters — Sterile and single-use catheters	No implant (technical)
ISO 10651 (all parts), Lung ventilators for medical use — Particular requirements for basic safety and essential performance	No implant

ISO standard	Exclusion reason, inclusion/check
ISO 10993 (all parts), Biological evaluation of medical devices	No CIC
ISO 11040 (all parts), Prefilled syringes	No implant
ISO/IEEE 11073 (all parts), Health informatics — Personal health device communication	No implant
ISO 11135 (all parts), Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices	No implant
ISO 11137 (all parts), Sterilization of health care products — Radiation	No implant
ISO 11138 (all parts), Sterilization of health care products — Biological indicators	No implant
ISO 11140 (all parts), Sterilization of health care products — Chemical indicators	No implant
ISO 11197, Medical supply units	No implant
ISO 11318, Cardiac defibrillators — Connector assembly DF-1 for implantable defibrillators — Dimensions and test requirements	No CIC
ISO 11607 (all parts), Packaging for terminally sterilized medical devices	No implant
ISO 11608 (all parts), Needle-based injection systems for medical use — Requirements and test methods	No implant
ISO 11663, Quality of dialysis fluid for haemodialysis and related therapies	No implant
ISO 11737 (all parts), Sterilization of medical devices — Microbiological methods	No implant
ISO/TS 13004, Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method VDmaxSD	No implant
ISO 13402, Surgical and dental hand instruments — Determination of resistance against autoclaving, corrosion and thermal exposure	No implant
ISO 13408 (all parts), Aseptic processing of health care products	No implant
ISO 13485, Medical devices — Quality management systems — Requirements for regulatory purposes	No CIC
ISO 13779 (all parts), Implants for surgery — Hydroxyapatite	No CIC (technical)
ISO 13782, Implants for surgery — Metallic materials — Unalloyed tantalum for surgical implant applications	No CIC (technical)

ISO standard	Exclusion reason, inclusion/check
ISO 13958, Concentrates for haemodialysis and related therapies	No implant
ISO 13959, Water for haemodialysis and related therapies	No implant
ISO 14155, Clinical investigation of medical devices for human subjects — Good clinical practice	YES
ISO 14160, Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices	No implant
ISO 14161, Sterilization of health care products — Biological indicators — Guidance for the selection, use and interpretation of results	No implant
ISO 14242 (all parts), Implants for surgery — Wear of total hip-joint prostheses	No CIC (technical)
ISO 14243 (all parts), Implants for surgery — Wear of total knee-joint prostheses	No CIC (technical)
ISO 14408, 0Tracheal tubes designed for laser surgery — Requirements for marking and accompanying information	No implant
ISO 14457, Dentistry — Handpieces and motors	No implant
ISO 14602, Non-active surgical implants — Implants for osteosynthesis — Particular requirements	Check chapter 7.3 clinical evaluation
ISO 14607, Non-active surgical implants — Mammary implants — Particular requirements	Check chapter 7.3 clinical evaluation
ISO 14630, Non-active surgical implants — General requirements	Check chapter 7.3 clinical evaluation
ISO 14644, Cleanrooms and associated controlled environments	No implant
ISO 14698, Cleanrooms and associated controlled environments — Biocontamination control	No implant
ISO 14708 (all parts), Implants for surgery — Active implantable medical devices Part 5 on circulatory support devices has a part a chapter 6.14 on clinical evaluation	No CIC
ISO 14879, Implants for surgery — Total knee-joint prostheses	No CIC (technical)

ISO standard	Exclusion reason, inclusion/check
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	No implant
ISO/TR 14969, Medical devices — Quality management systems — Guidance on the application of ISO 13485: 2003	No CIC
ISO 14971, Medical devices — Application of risk management to medical devices	Check
ISO 15001, Anaesthetic and respiratory equipment — Compatibility with oxygen	No implant
ISO 15002, Flow-metering devices for connection to terminal units of medical gas pipeline systems	No implant
ISO 15223-1, Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements	No CIC
ISO 15882, Sterilization of health care products — Chemical indicators — Guidance for selection, use and interpretation of results	No implant
ISO 15883 (all parts), Washer-disinfectors	No implant
ISO 15985, Plastics — Determination of the ultimate anaerobic biodegradation under high-solids anaerobic-digestion conditions — Method by analysis of released biogas	No implant
ISO 16061, Instrumentation for use in association with non-active surgical implants — General requirements	No implant
ISO 17510, Medical devices — Sleep apnoea breathing therapy — Masks and application accessories	No implant
ISO 17664, Sterilization of medical devices — Information to be provided by the manufacturer for the processing of resterilizable medical devices	No implant
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	No implant
ISO 18472, Sterilization of health care products — Biological and chemical indicators — Test equipment	No implant
ISO 18777, Transportable liquid oxygen systems for medical use — Particular requirements	No implant

ISO standard	Exclusion reason, inclusion/check
ISO 18778, Respiratory equipment — Infant monitors — Particular requirements	No implant
ISO 19054, Rail systems for supporting medical equipment	No implant
ISO 20857, Sterilization of health care products — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices	No implant
ISO 21534, Non-active surgical implants — Joint replacement implants — Particular requirements	No CIC, technical
ISO 21535, Non-active surgical implants — Joint replacement implants — Specific requirements for hip-joint replacement implants	No CIC, preclinical
ISO 21536, Non-active surgical implants — Joint replacement implants — Specific requirements for knee-joint replacement implants	No CIC, preclinical
ISO 21649, Needle-free injectors for medical use — Requirements and test methods	No implant
ISO 21969, High-pressure flexible connections for use with medical gas systems	No implant
ISO 22442 (all parts), Medical devices utilizing animal tissues and their derivatives	No CIC
ISO 22523, External limb prostheses and external orthoses — Requirements and test methods	No CIC
ISO 22610, Surgical drapes, gowns and clean air suits, used as medical devices, for patients, clinical staff and equipment — Test method to determine the resistance to wet bacterial penetration	No implant
ISO 22612, Clothing for protection against infectious agents — Test method for resistance to dry microbial penetration	No implant
ISO 22675, Prosthetics — Testing of ankle-foot devices and foot units — Requirements and test methods	No CIC
ISO 23328 (all parts), Breathing system filters for anaesthetic and respiratory use	No implant
ISO 23500, Guidance for the preparation and quality management of fluids for haemodialysis and related therapies	No implant

ISO standard	Exclusion reason, inclusion/check
ISO 23747, Anaesthetic and respiratory equipment — Peak expiratory flow meters for the assessment of pulmonary function in spontaneously breathing humans	No implant
ISO 23907, Sharps injury protection — Requirements and test methods — Sharps containers	No implant
ISO 23908, Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	No implant
ISO/TR 24971, Medical devices — Guidance on the application of ISO 14971	Check together with 14971
ISO 25424, Sterilization of medical devices — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices	No implant
ISO 25539 (all parts), Cardiovascular implants — Endovascular devices	Check, parts 1- 2- contain chapter 8.7 on clinical evaluation Part 3 No technical
ISO 26722, Water treatment equipment for haemodialysis applications and related therapies	No implant
ISO 27186, Active implantable medical devices — Four-pole connector system for implantable cardiac rhythm management devices - Dimensional and test requirements	No CIC (technical)
ISO 80369 (all parts), Small-bore connectors for liquids and gases in healthcare applications	No implant
ISO 81060 (all parts), Non-invasive sphygmomanometers	No implant
ISO/IEC 15026 (all parts), Systems and software engineering — Systems and software assurance	No complete implant
IEC/ISO 80601-2, Medical electrical equipment	No implant

CIC: clinical investigation chapter, ISO: International Organization for Standardization.
Grey: Included for full text check.

Table 34. Six ISO standards identified as potentially relevant out of 451 hits in ISO online search in the technical sector "Health, medicine and laboratory equipment", years 2016-2021 with the term "medical device" in the search window

ISO standard	Exclusion reason, inclusion/check
ISO/TR 12417-2:2017(en) Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 2: Local regulatory information	Check
ISO 5910:2018(en) Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices. A new version is under development (see e-mail Alan)	Check chapter 7.4 on clinical investigation
ISO/TR 14283:2018(en) Implants for surgery — Essential principles of safety and performance	Check chapter 5.14 on clinical evaluation
ISO/TS 17137:2019(en) Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants	Check Chapter 5.4 on clinical evaluation
ISO 16054:2019(en) Implants for surgery — Minimum data sets for surgical implants	Not about pivotal trials
ISO/TR 20416:2020(en) Medical devices — Post-market surveillance for manufacturers	Not about pivotal trials

ISO: International Organization for Standardization. Light grey = included for full text check

Table 35. Four ISO standards with a chapter on clinical investigation additionally identified out of 109 by search term "clinical investigation"

ISO standard	Exclusion reason, inclusion/check
ISO 11979-7:2018 Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations of intraocular lenses for the correction of aphakia	Wrong indication
ISO 11979-10:2018 Ophthalmic implants — Intraocular lenses — Part 10: Clinical investigations of intraocular lenses for correction of ametropia in phakic eyes	Wrong indication

ISO standard	Exclusion reason, inclusion/check
ISO 15798:2013(en) Ophthalmic implants — Ophthalmic viscosurgical devices.	Wrong indication
ISO/TR 22979:2017 Ophthalmic implants — Intraocular lenses — Guidance on assessment of the need for clinical investigation of intraocular lens design modifications	Wrong indication

ISO: International Organization for Standardization.

Table 36. List of 17 ISO standards selected from Table 33, Table 34, checked for relevance in full text

ISO Standard	Relevant text part	Relevant Information Yes/No/Reason*
ISO 5840-1:2021(en) Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements	Chapter 7.4	Yes, section 7.4 contains reference to ISO 14155 but Annex L contains suitable clinical investigation endpoints
ISO 5840-2:2021(en) Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes	Chapter 7.4	Yes, section 7.4 contains study design info in depth information and relevant annexes
ISO 5840-3:2021(en) Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques	Chapter 7.4	Yes, section 7.4 contains study design info in depth information and Annex G contains adverse event reporting in clinical investigations
ISO 5841-2 Implants for surgery — Cardiac pacemakers Part 2: Reporting of clinical performance of populations of pulse generators or leads		No, limited information on clinical investigations some reference to statistical guidelines

ISO Standard	Relevant text part	Relevant Information Yes/No/Reason*
ISO 5910:2018(en) Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices.	Chapter 7.4 on clinical investigation	Yes, study design details provided including data acquisition (PMCF Considerations included too)
ISO 7198: 2016, Cardiovascular implants — Tubular vascular prostheses	Clause 10.1 on clinical investigation	Yes, study design details provided including data acquisition.
ISO/TR 12417-2:2017(en) Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 2: Local regulatory information		No, points back to Medical Devices Directive.
ISO 14155: 2020 ISO 14155, Clinical investigation of medical devices for human subjects — Good clinical practice	Whole document	Yes
ISO/TR 14283:2018(en) Implants for surgery — Essential principles of safety and performance	Chapter 5.14 on clinical evaluation	No, points back to ISO 14155 and contains only 0.5 pages on clinical evaluation
ISO 14602 (2010), Non-active surgical implants — Implants for osteosynthesis — Particular requirements	Chapter 7.3 clinical evaluation	No, points to ISO 14630
ISO 14607, Non-active surgical implants — Mammary implants — Particular requirements	Chapter 7.3 clinical evaluation	No, only technical information is reported
ISO 14630 (2012), Non-active surgical implants — General requirements	Chapter 7.3 clinical evaluation	No, only a short part on clinical evaluation stating that data from literature reviews or from clinical investigations can be used, or both

ISO Standard	Relevant text part	Relevant Information Yes/No/Reason*
ISO 14971 (2020), Medical devices — Application of risk management to medical devices	e. g. chapter benefit-risk assessment	Yes, this standard is essential to understand the link between residual risk concept and "adequate clinical evidence" linked with different device characteristics
ISO/TS 17137:2021 (en) Cardiovascular implants and extracorporeal systems — Cardiovascular absorbable implants	Chapter 5.4 on clinical evaluation	Yes, study design details provided including data acquisition.
ISO/TR 24971 (2020), Medical devices — Guidance on the application of ISO 14971		Yes, complementary to the standard.
ISO 25539-1 (2017), Cardiovascular implants — Endovascular devices	Chapter 8.7 on clinical evaluation	Yes, study design details provided including data acquisition.
ISO 25539-2 (2020), Cardiovascular implants — Endovascular devices	Chapter 8.7 on clinical evaluation	Yes, study design details provided including data acquisition.
ISO/DIS 12417-1: (2021) Cardiovascular implants and extracorporeal systems — Vascular device-drug combination products — Part 1: General requirements	Identified from ISO 17137	Yes, study design details provided

ISO: International Organization for Standardization, light grey: included for data abstraction.

A.3 Search on Websites of National Regulatory Authorities, the Medical Devices Coordination Group, and the International Medical Device Regulators Forum

On the websites of the 27 EU member states national regulatory authorities responsible to implement the MDR (see list in appendix) we checked and searched the text for information on medical device regulation and clinical investigations and as well in documents available there when the topic was clinical investigation / clinical trials. If there was no separate section on this topic, we searched sections referring to medical device regulation or other sections and used “clinical trial”, clinical investigation” as search terms. We used the English version of the websites if available, but we also checked the websites in the national language. If we found additional information, we used “google translator” to translate the texts into English. Searches were performed between June and November 2021. We checked the websites that had technical problems or where we did not find information on interesting topics 2-3 times.

We also searched the websites of regulatory authorities responsible for medical devices of the following Non-EU countries: Australia, Canada, Japan, Norway, Switzerland, UK, USA.

Table 37. Selection of regulatory documents from national websites search on June 15 (Belgium-Netherlands) /16 (Poland-United Kingdom and Austria), 2021 17.6.: Canada, USA, additional searches, where indicated in Oct. and Nov. 2021.

Country	Website	Date	Document title / number / comments	Inclusion status
Austria	Federal Ministry of Health BASG - Austrian Federal Office for Safety in Health Care Surveillance / AGES – Austrian Medicines & Medical Devices Agency https://www.basg.gv.at/gesundheitsberufe/klinische-studien/klinische-pruefung-medizinprodukte	16.6.21	„Leitfaden zur Einreichung und Durchführung von Klinischen Prüfungen von Medizinprodukten (MP) und LBP von IVD (IVD)“ gültig ab 02.10.2020 AGES always refers to BASG. Available doc on clinical investigation according to MEDDEV contains no recommendation on GCP, but refers in Annex III to ISO 14155 and 14971, to MEDDEV guidance, and the Austrian “Medizinproduktegesetz”. Announces guidance and documents for clinical trials according to MDR (in preparation)	No relevant guidance documents
Belgium	Belgium Federal agency for medicines and health products (FAMPH) https://www.famhp.be/en/human_use/health_products/medical_devices_accessories/clinical_evaluation/DM_AIMD	15.6.21	“Clinical investigations – Guidance on Dossier Content” version 2 published 7.6.21 which e. g. lists content that is needed for the dossier such as characterization of study design. The document mainly refers to ISO 14155:2020 but modifies the recommendations of ISO at some points. **Included.** “Information on investigational medical devices according to section 2.7 of chapter II of annex XV MDR” lists a matrix of general safety and performance requirements in column 1 and asks to fill in standards and common specifications used in column 3, evidence of conformance in column 4 and a justification in case of deviation in column 5. **Excluded** “Guideline Submission Processes of Clinical Investigations according to MDR in Belgium” version 4 7.6.21 gives guidance on how to decide which is the right regulatory pathway and on the processes in Belgium. **Excluded**	1 document included “Clinical investigations – Guidance on Dossier Content” version 2 published 7.6.21

Country	Website	Date	Document title / number / comments	Inclusion status
Bulgaria	Bulgarian Drug Agency https://www.bda.bg/en/administrative-services https://www.bda.bg/en/information-for-companies/114-medical-devices-category	15.6.21 25.10.21 15.11.21	On website MDR announced as implemented. On the website for companies with regard to clinical trials, there are several application forms in Bulgarian (translated by Microsoft translator) for trial authorization, but no documents on GCP, no references to GCP (guidance docs). It is unclear whether these docs are already related to MDR.	No relevant documents
Croatia	Croatia Agency for Medicinal Products and Medical Devices https://www.halmed.hr/en/Medicinski-proizvodi/ https://www.halmed.hr/en/Medicinski-proizvodi/Upute-za-podnositelje-zahtjeva-41/Proizvodnja-medicinskih-proizvoda/	15.6.21 25.10.21	Role of agency with regards to MD described, no regulatory documents related to MDR, Medical Devices Act relates to MDD, no document on clinical trials and GCP.	No relevant documents
Cyprus	Cyprus Medical Devices Competent authority https://www.moh.gov.cy/moh/mphs/mphs.nsf/page21_em/page21_em?OpenDocument	15.6.21 25.10.21	Refers to MDR under “Start a Clinical Investigation/Performance in Cyprus” and also to the Directives and the MDR under “Regulatory Information: general legislation and guidelines”.	No relevant documents
Czech republic	Ministry of Health of the Czech Republic Dep.of Pharmacy https://www.mzcr.cz/en/the-ministry-of-health/	15.6.21 25.10.21	No information on medical devices retrieved	No relevant documents

Country	Website	Date	Document title / number / comments	Inclusion status
Denmark	Danish Medicines Agency https://laegemiddelstyrelsen.dk/en/devices/	15.6.21 25.10.21 15.11.21	Website on clinical trials (available only in Danish language) refers to ISO 14155:2020 and guidance from the MDCG on reporting on serious adverse events and to MDCG guidance that is in preparation. Website on MD legislation refers to executive order no 957 of 29 April 2021, which implements MDR 2017/745 in Danish law. Does not contain guidance on trial design.	No relevant guidance documents
Estonia	Estonia Health Board Medical Devices Department https://www.terviseamet.ee/en/medical-devices	15.6.21 25.10.21	Website on legislative framework outdated (2016), no regulatory documents to MDR, no documents on clinical investigations	No relevant documents
Finland	Finland National supervisory Authority for Welfare and Health, Valvira and Fimea https://www.valvira.fi/web/en/valvira/about-this-site https://www.fimea.fi/web/en/medical-devices	25.10.21 15.11.21	Home page on clinical investigations refers to MDCG 2021-06 and 2021-08, also Finish part for applications to FIMEA refers to MDCGs. In a draft guidance document for application for authorization of clinical trials to FIMEA published in November 2021 available only in Finish there is also a reference to ISO 14155:2020	No relevant documents
France	Agence nationale de sécurité du médicament et des produits de santé (ANSM) Ministère des solidarités et de la santé (DGS) https://ansm.sante.fr/documents/reference/reglementation-relative-	25.10.21	Home page on clinical investigations refers to relevant MDCG documents Heading “Regulation of MDs and IVDs relating to clinical investigations and research involving humans” refers to National Public Health Code which seems to have no part on good clinical practice. Reference documents on GCP did not contain a GCP on medical devices clinical investigations.	No relevant documents

Country	Website	Date	Document title / number / comments	Inclusion status
	aux-essais-ou-investigations-cliniques/reglementation-des-dm-et-dmdiv-relative-aux-recherches-impliquant-la-personne-humain			
Germany	Germany Federal Ministry of Health Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG) https://www.zlg.de/medizinprodukte https://www.zlg.de/medizinprodukte/dokumente Bundesinstitut für Arzneimittel und Medizinprodukte https://www.bfarm.de/DE/Medizinprodukte/_node.html	15.6.21 25.10.21 16.11.21	Two Institutions, ZLG and BfArM, are responsible for issues on medical device regulation. ZLG has oversight on NB. GCP documents not in the obligation of ZLG, no relevant documents. BfArM answers FAQs with regard to regulation of clinical investigations, reference to contact person. The „Medizinproduktedurchführungs-gesetz“ (MPDG) transforms the MDR in national law. It is, especially in case of clinical investigations, stricter than the MDR (data protection, persons allowed to take part, interaction with Ethics Committee etc, but no relation to GCP). BfArM- website on “Klinische Prüfungen und Leistungsbewertungen” references to “Medizinproduktegesetz”, in which all paragraphs are deleted in the newest version, and to „Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten (Medizinprodukte-Anwendermelde- und Informationsverordnung-MPAMIV)“, which was adapted to MDR. The section on the request for authorisation only applies to IVD, for MD the MPDG applies. The MPDG only references to the MDR, not to GCP / ISO. With regard to regulatory framework link to EU website on medical devices. Servicetelefon Montag, Dienstag und Donnerstag von 9 bis 11.30 Uhr Telefon: +49 (0)228 99 307-5999 bzw. 0228 207 3975	No relevant documents
Greece	Greece National Organization for Medicines (EOF)	15.6.21 27.10.21	One document refers to practical issues for clinical research with regard to MDR 2017/745. Does not contain GCP.	No relevant documents

Country	Website	Date	Document title / number / comments	Inclusion status
	https://www.eof.gr/web/guest/medicaldevices			
Hungary	Hungary National Institute of Pharmacy and Nutrition https://ogyei.gov.hu/about_us	15.6.21 27.10.21	No information on regulatory affairs on medical devices found, last update of home page on 12.06.2019	No relevant documents
Ireland	Ireland Health Product Regulatory Authority (HPRA) https://www.hpra.ie/homepage/medical-devices	15.6.21 27.10.21	The document "Guide to Clinical Investigations Carried Out in Ireland" references for GPC ISO 14155: 2020, and MDCG guidance documents	No relevant guidance document
Italy	Italy Ministry of Health https://www.salute.gov.it/portale/temi/p2_3_dispositivi.html	15.6.21 27.10.21	Circular of MoH explains impact of MDR on clinical investigations. No reference to GCP documents. 2 documents on procedural requirements for clinical investigations for different risk classes. Further documents in reference list, they do not refer to GCP. Application forms for clinical trials do not directly reference to MDCG or ISO 14155, but they contain partly ISO 14155 classification of development stages (pilpt. Pivotal, post-market) and design types explanatory, confirmatory, observational.	No relevant guidance document
Latvia	Latvia Ministry of Health https://www.vm.gov.lv/lv	15.6.21 27.10.21	The document "Procedures for Registration, Conformity Assessment, Distribution, Operation and Technical Supervision of Medical Devices" does not contain guidance on GCP of clinical investigations, and it refers to the MDD (90/385, 93/42 etc.) No legislation on implementation of MDR found.	No relevant guidance document
Lithuania	Lithuania State Health Care Accreditation Agency under the Ministry of Health	15.6.21 27.10.21	The document "APPROVAL OF THE DESCRIPTION OF THE PROCEDURE FOR THE AUTHORIZATION OF A CLINICAL TRIAL WITH A MEDICAL DEVICE" refers to MDR and does not contain guidance on GCP of clinical investigations	No relevant guidance document

Country	Website	Date	Document title / number / comments	Inclusion status
	https://vaspvt.gov.lt/en			
Luxembourg	Luxembourg Ministère de la Santé https://sante.public.lu/fr/index.php	15.6.21 27.10.21	No legislation on implementation of MDR found.	No up-to-date legislation on implementation of MDR found.
Malta	Malta Competition and Consumer Affairs Authority https://mccaa.org.mt/	15.6.21 27.10.21	No sector for medical devices, no documents	No documents
Netherlands	Health & Youth Care Inspectorate https://english.igj.nl/medical-technology Ministry of Health, Welfare & Sports https://www.government.nl/ministries/ministry-of-health-welfare-and-sport	15.6.21 27.10.21	The document on "Medical Research Involving Humans Act" and the amending law to implement MDR and IVDR in the medical research act only contains general statements on research methodology such as "the research meets the requirements of a correct methodology of scientific research". No documents on GCP of medical devices.	No relevant guidance document
Poland	The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products http://www.urpl.gov.pl/en/medical-devices	16.6.21 27.10.21	No relevant documents on legislation of MDR	No relevant documents

Country	Website	Date	Document title / number / comments	Inclusion status
Portugal	National Authority of Medicines and Health Products, IP. (INFARMED) https://www.infarmed.pt/web/infarmed-en/medical-devices	16.6.21 27.10.21 15.11.21	Document "Guide for regulatory and scientific advice" contains no reference to GCP. Link to the document was broken on 27.10.21 Information referring to MD were basic and only related to the MDD. No relevant documents on legislation of MDR	No relevant documents
Romania	National Agency for Medicines and Medical Devices https://www.anm.ro/en/dispozitive-medicale/	16.6.21 27.10.21 15.11.21	Document on clinical investigation is related to the MDD ("The relevant provisions of annex no. 10 of the directives remain applicable") and contains no recommendations.	No relevant documents
Slovakia	State Institute for drug control (Medical Devices Section) https://www.sukl.eu/medical-devices/clinical-evaluation-of-medical-devices	16.6.21 16.11.21	The text on "application for authorisation of clinical investigation conduct" seems to refer to the MDD, date of website is 1.7.2015. Different documents on how to apply for clinical investigations, but no GCP guidelines. No regulatory documents with reference to MDR.	No relevant guidance document
Slovenia	Agency for medicinal products and medical devices of the Republic of Slovenia https://www.jazmp.si/en/	15.11.21	Medical device section of the website of the agency provided an error 404 message. By searching with the term "medical device" on the website, a short text was found that the JAZMP is the competent authority for MD. No regulatory documents with reference to MDR.	No relevant documents found
Spain	Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS)	16.6.21 28.10.21	The document circular 7/2004 refers to the MDD and contains statements on the methodology of clinical investigations and relates to a former version of ISO 14155. No regulatory documents with reference to MDR.	No relevant guidance document

Country	Website	Date	Document title / number / comments	Inclusion status
	https://www.aemps.gob.es/productossanitarios/productossanitarios_prodsanitarios/			
Sweden	Medical Products Agency https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/clinical-investigation-of-medical-devices#hmainbody1	16.6.21 28.10.21	Broken link to the document on "Application and notification of clinical investigations". Section "Good Clinical Practice" refers to ISO 14155 latest published version (2020)	No relevant guidance document
EFTA countries and UK				
Norway	Directorate of Health – Norway https://legemiddelverket.no/english/medical-devices/regulatory-information-regarding-medical-devices/clinical-investigation-of-medical-devices	16.6.21 28.10.21 17.11.21	Docs that announce implementation of MDR in Norwegian law, references to guidance by MDCG, no docs on good clinical practice of clinical investigations	No relevant guidance document
Swissmedic	Swissmedic, Swiss Agency for Therapeutic Products https://www.swissmedic.ch/swissmedic/en/home/medical-devices/klinische-versuche/bewilligungsverfahren.html	16.6.21 28.10.21 17.11.21	MDR was intended to be implemented into Swiss law, but negotiations on Mutual Recognition Agreement between EU and Switzerland have failed. Switzerland adapted the legislation on MD regulation. This will result mainly in no access to EUDAMED for Switzerland and therefore additional registration and reporting in Switzerland was included in the legislation, but changes have no relevance for GCP. The "Information sheet on clinical trials in Switzerland" is the document with the most concrete statements regarding clinical trials. It references to ISO 14155 (without version number), MDR and MDGC 2020-10. The remaining text is on procedures.	No relevant guidance document

Country	Website	Date	Document title / number / comments	Inclusion status
			The form for the application authorisation of clinical trials contains a part on the characteristics of type of trial: "Trial with clinically relevant primary endpoints, defined statistical hypotheses and pass/fail criteria, level of significance and statistically justified calculation of the number of trial subjects (according to international standard EN ISO 14155)"	
United Kingdom	United Kingdom Medicines & Healthcare products Regulatory Agency https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety	16.6.21 28.10.21	MDR will not be implemented in UK, but Northern Ireland has to apply the EU MDR. The 3 MDD have already been implemented 2002 in UK law and are still valid. The Medicines and Medical Devices Act from March 2021, "introduces targeted delegated powers in the fields of human medicines, veterinary medicines and medical devices to enable the existing regulatory frameworks to be updated following the United Kingdom's (UK) departure from the European Union (EU);" and several other issues to adapt to the situation after Brexit. The MDR 2002 has been updated. There is a list of changes in the appendix. Other changes that are still to implement are mentioned on the home page. 3 of the following 5 guidance documents on legislation contain more detailed guidance on trial design. "Clinical investigations of medical devices – compiling a submission to MHRA, May 2021" refers also to ISO 14155: 2020 for CIP and IB but lists (at least) reporting requirements. "Clinical investigations of medical devices – guidance for manufacturers, May 2021" contains recommendations on trial design. "Clinical investigations of medical devices – guidance for investigators, May 2021" refers only to ISO 14155: 2020 and the guidance to manufacturers above without further details.	3 documents with recommendations on trial design included

Country	Website	Date	Document title / number / comments	Inclusion status
			"Clinical investigations of medical devices – statistical considerations, May 2021" contains recommendations on trial design. "Guidance on applying human factors and usability engineering to medical devices including drug-device combination products in Great Britain. Version 2.0, January 2021". In general, human factors may contribute to the benefit-risk-relation, but these studies are not part of a quantitative clinical trial. Usability engineering uses qualitative research design.	
North America, Australia, Japan				
Canada	Health Canada Medical Devices Bureau of the Therapeutic Products Directorate (TPD) https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices.html	17.6.21 28.10.21 07.07.22	Guidance document "Applications for Medical Device Investigational Testing Authorizations, Effective Date 2018/10/01." With regard to GCP and trial design it refers to ISO 14155, but also to ICH guidelines. Sparse recommendations on trial design. EXCLUDED BECAUSE EVIDENCE REQUIREMENTS FOR ITA are not the same as for licence application. In the "list of recognized standards", 2021 the old version ISO 14155: 2011 is listed, not the actual one. The document: "Considerations for inclusion of women in clinical trials and analysis of sex differences", 2013 is included. It does not contain further recommendations except on inclusion of women in the study population. The document: "Guidance on supporting evidence to be provided for new and amended licence applications for Class III and Class IV medical devices, not including In Vitro Diagnostic Devices (IVDDs), 2012" gives no guidance on trial design and was excluded. Document: "Guidance for the Interpretation of Significant Change of a Medical Device", 2011. A significant change requires an application for an amendment	1 document included

Country	Website	Date	Document title / number / comments	Inclusion status
			of the medical device licence. Excluded, because evidence requirements for an amendment are not covered. "Guidance on how to complete the application for a new medical device licence", 2021 was excluded, because it contained no recommendations on trial design. A device-specific guidance document was retrieved, but excluded, because it's too old: "Pre-market guidance on bare cardiovascular stents", 2004 Under Guidance documents there is a notice that guidance documents from the FDA in the USA should be used if there is no guidance on the same subject from TPD.	
USA	U.S. Food and Drug Administration https://www.fda.gov/regulatory-information/search-fda-guidance-documents	17.6.21 3.11.21 27.1.22	Searched all clinical trial guidance documents on 3.11. (130) and additionally screened newly published guidance documents , selected 8 documents on general design issues of MD trials to include: 1."Design Considerations for Pivotal Clinical Investigations for Medical Devices", 2013; 2. "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials", 2010; 3. "Adaptive Designs for Medical Device Clinical Studies", 2016;4. "Evaluation of Sex-Specific Data in Medical Device Clinical Studies", 2014; 5. "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies", 2017; 6. "CDRH Health of Women Strategic plan", Jan 2022; 7. "Patient Engagement in the Design and Conduct of Medical Device Clinical Studies", 2022 The document 8. "Collection of Race and Ethnicity Data in Clinical Trials." was identified by the citation in 5. "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies" and additionally	Overall, 11 documents with recommendations on trial design or evaluation of the benefit-risk balance or substantial equivalence included

Country	Website	Date	Document title / number / comments	Inclusion status
			included, because it contains the nomenclature to ask for, describe and report race and ethnicity in clinical trials. 2 further documents on the principles of the benefit-risk determination were included: ”Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications”, 2019; “Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions”, 2019. With regard to 510k notifications 1 document has been included: “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications”, 2014. Contains determination of substantial equivalence With regard to device-specific guidance 3 documents were retrieved in the field of cardiovascular, orthopaedic or diabetes devices: “Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation”, 2004; “Clinical Study Designs for Catheter Ablation Devices for Treatment of Atrial Flutter”, 2008; “Clinical Study Designs for Surgical Ablation Devices for Treatment of Atrial Fibrillation”, 2004. We excluded these documents because they might be outdated in this rapidly developing field Device-specific guidance on other specialities (e. g. for prostate or urinary tract related health problems, and neurological diseases) were excluded. ”Changes or modifications during the conduct of a clinical investigation”, 2001 was excluded, because contains no relevant recommendation on trial design. It explains when a manufacturer has to submit a supplement to FDA, notify or include information in the annual progress report of the clinical investigation	

Country	Website	Date	Document title / number / comments	Inclusion status
			when changes or modifications in the investigational device or the study protocol are made during a clinical investigation. "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations", Dec 2021; excluded because concerns a too specific issue of data collection. "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval", 2015 excluded because no recommendations on trial design of pivotal trials but examples under which conditions certain questions on effectiveness or safety can be addressed by post-market data. "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices", 2017, was excluded because it is only mentioned that RWE among other reasons can also be used in the context of pre-market approval but contains no recommendations on trial design. "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions", 2017 excluded, because no recommendations on trial design, benefit-risk evaluation is related only to study authorisation, not to market approval. "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation"; 2022 was excluded, because this is part of another task of WP1 of CORE-MD	
Australia	Department of Health, Therapeutic Goods Administration https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd	17.6.21 3.11.21 5.11.21 19.11.21	Checked all guidance documents on the website under heading clinical trials. 2 documents were checked in detail: "Australian clinical trial handbook", 2021 applies to medicinal products and medical devices. For GCP ISO 14155: 2020 is considered the relevant guidance for MD trials. There are no further specifications.	1 document included

Country	Website	Date	Document title / number / comments	Inclusion status
		7.07.22	The following document was included: "Clinical evidence guidelines. Medical devices version 3", Nov 2021. Updated Version 3.1 June 2022. Applying ISO 14155 is required, the document also contains detailed guidance on the clinical evaluation report (CER) and specific issues such as substantially equivalent devices, and device-specific guidance. Contains "should" statements with regard to trial design refers also to standards of study type specific reporting guidelines, IMDRF documents on clinical investigation, clinical evaluation and key definitions for clinical data, and MEDDEV 2.7/1 Revision 4.	
Japan	Ministry of Health, Labour and Welfare https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/index.html Pharmaceuticals and Medical Devices Agency https://www.pmda.go.jp/english/index.html	17.6.21 3.11.21	"Ministerial Ordinance on Good Clinical Practice for Medical Devices" from 2009 does not contain recommendations on trial design. "Points to Consider When Applying for Marketing Approval for Medical Devices", 2005 contains only very general recommendations such as use a sufficient sample size, excluded. "Release of Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices", 2017 contains recommendations on trial design e. g. for sample size, **included.** Under the heading "medical device standards" there are no downloadable documents. Under the heading "outcome documents of the scientific board" no relevant document on medical devices retrieved (except paediatric devices, which did not contain concrete recommendations on trial design, only the notion that the same principles should be applied as for adult use) Under "publications of PMDA staff" searched with "medical device" 1 article found: "New Regulatory Framework for Medical Devices in Japan: Current Regulatory Considerations Regarding Clinical	1 document included

Country	Website	Date	Document title / number / comments	Inclusion status
			Studies". This article generally describes the preconditions when premarket clinical trials can be substituted by post-market studies, but this is already described in the guidance document above.	

GCP: Good Clinical Practice

Further we searched the websites of the Medical Device Coordination Group (MDCG) and of the International Medical Devices Regulation Forum (IMDRF), but also checked the included documents of the national regulators for references to these two institutions.

Table 38. Selection of regulatory guidance documents from the European Commission, the Medical Device Coordination Group, and the International Medical Device Regulators Forum

Date of Search	Document number / title	Comments	Inclusion status
19.11.21 07.04.22 EC newsletter	MDCG 2019-9 Summary of safety and clinical performance A guide for manufacturers and notified bodies, August 2019 1st revision of MDCG 2019-9 in March 2022	Describes what should be included in the SSCP, contains a part on what and how to report the results of clinical evaluation and investigations	Included
19.11.21	MDCG 2020-3 Guidance on significant changes regarding the transitional provision under Article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD, March 2020	Defines what can be considered as a significant change in design or intended purpose of a device for legacy devices. Excluded because this is not in the context of a clinical investigation, but it is the condition when a legacy device cannot be marketed any longer under the MDR.	Excluded
19.11.21	MDCG 2020-05: Clinical evaluation – equivalence. A guide for manufacturers and notified bodies, April 2020	Is characterised as best practice document in introduction. ”MEDDEV 2.7/1 rev. 4 should be used also during demonstrating equivalence under the MDR. […In cases of divergence between the MEDDEV 2.7/1 rev. 4, this MDCG guidance and the MDR, the MDR shall take precedence].” The MDCG 2020-05 compares text of MDR and MEDDEV 2.71 rev. 4. on the equivalence of technical, biological, clinical characteristics of the device with explanations how certain terms are to interpret (e. g. similar, same). Meaning of demonstration of equivalence is explained also with regard of necessary clinical evidence. Explanation for different types of MD. Table in Annex how to present the evaluation of equivalence.	Included

Date of Search	Document number / title	Comments	Inclusion status
19.11.21	MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies, April 2020	"[This guidance document] intends to support a harmonized approach with respect to clinical data providing sufficient clinical evidence necessary to demonstrate conformity with the relevant General Safety and Performance Requirements (GSPR) across European Union Member States." Definitions for terms not defined in MDR "legacy device", "well-established technology", "scientific validity", "level of clinical evidence", "state-of-the art", "intended use", "indication", "similar device". Appendix I lists sections of MEDDEV 2.7/1 rev. 4 relevant to the MDR Appendix III suggests a hierarchy of clinical evidence for confirmation of conformity with General Safety and Performance Requirements (GSPR)	Included
19.11.21	MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745, May 2020 and MDCG 2020-10/2 clinical investigation summary safety report form v1.0	The document provides guidance for safety reporting under MDR for the transition period until Eudamed will be available for safety reporting in clinical investigations performed in the EU member states and in third countries in which a clinical investigation is performed under the same clinical investigation plan. Defines serious adverse events and categories of causality and what must be reported to the relevant authorities. Provides a form for reporting that must be used."	Included
19.11.21	MDCG 2020-13 Clinical evaluation assessment report template, July 2020	The CEAR is "used by the NB to clearly document the conclusions of its assessment of the clinical evidence presented by the manufacturer in the CER and the related clinical evaluation that was conducted." The template should provide a standardized method for documenting the NB's assessment of the manufacturer's clinical evaluation. CEARs will also support specific additional requirements. Shows the criteria that NBs will have to apply for the assessment	Included

Date of Search	Document number / title	Comments	Inclusion status
6.12.21	MDCG 2021-05 Guidance on standardisation for medical devices, April 2021	Important background information on the general framework for harmonized European standards, but no guidance on trial methodology	Excluded
19.11.21	MDCG 2021-06 Q& A regarding clinical investigations, April 2021	Contains guidance on reporting of clinical investigations, and how a substantial modification of a trial is defined.	Included
19.11.21	MDCG 2021-08 Clinical investigation application/notification documents, May 2021 plus Annexes	Templates for clinical investigation application/notification documents for the time until EUDAMED will work. Annex 1 contains, a classification of trial designs and comparators, but without further guidance and definition. Annexes 2-6 do not contain further relevant information. Annexes 2-4 contains the same classifications as in Annex 1 for additional investigational devices, comparators, investigation sites Annex 5 contains a checklist list of mandatory and additional elements of an application. Annex 6 contains a table where the standards, common specifications or other GPSR used, should be listed.	Included
16.12.21	MDCG 2021-28 Substantial modification of clinical investigation under Medical Device Regulation, Dec 2021	This document provides a template with questions which the sponsor has to answer when s/he wants give notice of introducing substantial modifications to a clinical investigation that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation. But there is no guidance or criteria with regard to these issues.	Excluded

Date of Search	Document number / title	Comments	Inclusion status
19.11.21	MEDDEV 2.7/1 revision 4: Clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC, June 2016	As stated in MDCG-2020-05 this doc should be considered with regard to demonstrating equivalence. As stated in MDCG-2020-6 section 9.3.1 this doc should be considered with regard to evaluation of methodological quality and validity in MDD/AIMDD "which are equally valid under the MDR which can be considered to apply when referencing to 'scientific validity' as guidance." Appendix I of MDCG-2020-06 lists all parts of the MEDDEV 2.7/1 rev. 4 relevant to clinical evaluation for the MDR	Included
6.12.21	MEDDEV 2.7/2 revision 2: Guidelines on medical devices. Guidelines for competent authorities for making a validation assessment of a clinical investigation application under directives 93/42/EEC and 90/385/EEC, Sep 2015	Scope of the document: "This document provides guidance on: • description of the documents to be validated and/or assessed; • criteria to be applied for general validation/assessment; • description of events that may occur during the carrying out of the investigation and possible measures to be adopted; • specific aspects of assessment (criteria in Appendices)." The guidance refers to outdated ISO standards 14155: 2011, 14971: 2012, but considers methodological aspects of trial design for the decision on approval of the clinical investigation. Because of new regulation not applicable.	Excluded
6.12.2021	MEDDEV 2.7/4 Guidelines on clinical investigation: A guide for manufacturers and notified bodies, Dec 2010	Contains several recommendations regarding clinical data requirements and study design for medical devices, Cites [D.B. Kramer et al, American Journal of Therapeutics 17, 2-7 (2010)] for endpoint definition. Refers to outdated harmonized standard ISO 14155: 2009. Already published MDCG guidance documents partly substitute this guidance.	Excluded

Date of Search	Document number / title	Comments	Inclusion status
8.12.21	IMDRF Essential principles of safety and performance of 18 medical devices and IVD medical devices, Jan 2018	Has no recommendations on clinical trial design, refers to the declaration of Helsinki, GHTF/SG5/N1R8:2007 Clinical Evidence – Key Definitions and Concepts GHTF/SG5/N3:2010 clinical investigation, and ISO 14155. All cited documents are superseded by updated versions of IMDRF (see next 2 documents) or ISO documents	Excluded
8.12.21	IMDRF Clinical Investigation, Oct 2019	Scope: "guidance in relation to -when a clinical investigation should be undertaken for a medical device to demonstrate compliance with the relevant Essential principles […] -the general principles of clinical investigation involving medical devices." "Guidance […] is intended to apply to medical devices other than IVDDs […] was drafted primarily to address the use of Clinical Investigations to support a marketing authorization application." Takes over the relevant parts of MEDDEV 2.7/4	Included
8.12.21	IMDRF Clinical evidence- key definitions and concepts, Oct 2019	Contains definitions and explanations regarding the terms clinical evidence, clinical evaluation, clinical data and clinical investigation. Does not directly contain GCP for clinical investigations	Excluded
8.12.21	IMDRF Clinical evaluation, Oct 2019	Scope: "The primary purpose of this document is to provide manufacturers with guidance on how to conduct and document the clinical evaluation of a medical device as part of the conformity assessment procedure prior to placing a medical device on the market as well as to support its ongoing marketing. It is also intended to provide guidance to regulators and other stakeholders when assessing clinical evidence provided by manufacturers. This document provides the following guidance: · general principles of clinical evaluation;	Included

Date of Search	Document number / title	Comments	Inclusion status
		· how to identify relevant clinical data to be used in a clinical evaluation; · how to appraise and integrate clinical data into a summary; and · how to document a clinical evaluation in a clinical evaluation report." Contains guidance how a clinical investigation should be documented, appraised and analyzed. See Appendices. Compare with MEDDEV 2.7.1/rev 4	
9.12.21	IMDRF Principles of conformity assessment for medical devices, Nov 2012	Contains no recommendations on clinical investigations	Excluded
9.12.21	IMDRF terminologies for categorized adverse event reporting (AER): terms, terminology structure and codes, Mar 2020 plus Annexes A-G	Terminology of adverse events, included because it is an element of standardized outcome definitions in medical device trials	Included
9.12.21	IMDRF Methodological Principles in the Use of International Medical Device Registry Data, Mar 2017	Among other issues provides guidance on methodological principles in the clinical evaluation of performance/effectiveness and safety across the device life cycle using international Coordinated Registry Networks (iCRNs); Especially registry nested trials are mentioned. But this is only anecdotal and not elaborated.	Excluded
9.12.21	Statement regarding Use of ISO 14155:2011 "Clinical investigation of medical devices for human subjects – Good clinical practice", Mar 2015	Describes the role of the ISO 14155:2011 in the assessment of conformity in the member states of the IMDRF. Included only for this background information. Contains no recommendations on trial design	Excluded

Date of Search	Document number / title	Comments	Inclusion status
	Statement regarding Use of ISO 14971:2007 "Medical devices -- Application of risk management to medical devices", Oct 2015	Describes the role of the ISO 14971:2007 in the assessment of conformity in the member states of the IMDRF. Included only for this background information. Contains no recommendations on trial design	Excluded

A.4 Search on Websites of Regulatory–academic or Private Research Consortia dealing with Medical Devices Trial Designs

Table 39. Selection of Documents from Websites of Regulatory-private Research Consortia

Institution / country	Website	Date	Document title / number / Comments	Inclusion status
Medical Device Innovation Consortium/ USA	https://mdic.org/	31.01.22	We downloaded the following 4 documents: "National Evaluation System for health Technology Coordinating Center (NESTcc) Methods Framework", 2020; describes the research methodology for generating real-world evidence from real-world data for medical devices, premarket approval is also a subject. "External evidence methods (EEM) framework, draft", 2021; provides a framework and statistical methods for leveraging data from sources outside a prospectively designed study into a prospectively designed study to support regulatory decision-making. (included) "National Evaluation System for health Technology Coordinating Center (NESTcc). Methods Framework", 2020 is a " pragmatic methodological framework or "living playbook" that can be used by all stakeholders across the NESTcc medical device ecosystem in designing, executing, and evaluating research studies based on RWD. The Methods Framework is also intended to highlight device-specific considerations in benefit/risk studies based on both observational and experimental designs. While the Framework is closely linked to regulatory science, the principles described are applicable to any study intending to quantify cause and effect, and to descriptive studies." (included) "Patient centered benefit-risk project report: A Framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology", 2015;	2 included

Institution / country	Website	Date	Document title / number / Comments	Inclusion status
			specifies when patient information of their benefit- risk preferences are less or more valuable. "Maximizing patient input in the design and development of medical device clinical trials", 2021 focus on the input patients can give to determine outcomes and trial design issues especially relevant for device trials. Due to resource reasons, we excluded the topics related to patient involvement. We excluded Framework on data quality because it's too detailed.	
Clinical Trials Transformation Initiative/ USA	https://ctti-clinicaltrials.org/ (public-private partnership between FDA, and public authorities involved HTA, industry, universities)	31.01.22	Searched section "recommendations and resources". After using filter "recommendations" 34 docs available. 1 document: "CTTI recommendations: registry trials" included. Provides decision trees and checklists when a registry is appropriate to conduct trials. Mikita et al. „Determining the Suitability of Registries for Embedding Clinical Trials in the United States: A Project of the Clinical Trials Transformation Initiative". Ther Innov Regul Sci. 2021;55:6-18. Overall, no specific guidance on medical device trials found.	2 included
National Institute for Health /USA	https://rethinkingclinicaltrials.org/	31.01.22	No medical device specific guidance	0 included
Regulatory Horizons Council, United Kingdom	https://www.gov.uk/government/groups/regulator	20.01.22	Report on medical devices did not contain recommendations on trial design	0 included

Institution / country	Website	Date	Document title / number / Comments	Inclusion status
	y-horizons-council-rhc			

A.5 Appendix A from ISO 14155: 2020

Annex A from ISO 14155:2020 appears with the kind permission of Austrian Standards plus GmbH as a subsidiary of ISO member Austrian Standards International, Vienna.

Annex A(normative)Clinical investigation plan (CIP)

A.1 General

A.1.1 Introduction

This annex specifies the content of a CIP. If the required information is written in other documentation, for example the IB, such documentation shall be referenced in the CIP and shall be made available on request.

The content of a CIP and any subsequent amendments shall include all the topics listed in this annex, together with a justification for each topic if this is not self-explanatory.

NOTE Some requirements might not be applicable for exploratory and observational clinical investigations (see I.7).

A.1.2 Identification of the clinical investigation plan

a) Title of the clinical investigation.

b) Reference number identifying the specific clinical investigation, if any.

c) Version or date of the CIP.

d) Summary of the revision history in the case of amendments.

e) Version/issue number and reference number, if any, with the page number and the total number of pages on each page of the CIP.

f) Abbreviations and acronyms.

A.1.3 Sponsor

Name and address of the sponsor of the clinical investigation and information about funding source.

Certain national or regional regulations can require that if the sponsor is not resident in the country (countries) in which the clinical investigation is to be carried out, the name and address of a local representative who acts as the sponsor fulfilling responsibilities of the sponsor in that country (those countries) are provided.

A.1.4 Principal investigator, coordinating investigator and investigation site(s)

a) Name, address, contact details and professional position of

1) principal investigator(s),

2) coordinating investigator, if appointed.

b) Name and address of the investigation site(s) in which the clinical investigation will be conducted.

c) Name(s) and address(es) of external organizations (such as core laboratories, CROs, consultants or other contractors) involved in the clinical investigation.

The different roles, responsibilities and qualifications of investigators shall be specified. The sponsor shall maintain an updated list of principal investigators and investigation sites. This list can be kept separately from the CIP. The definitive list shall be provided with the clinical investigation report (see Annex D).

A.1.5 Overall synopsis of the clinical investigation

A summary or overview of the clinical investigation shall include all the relevant information regarding the clinical investigation design such as inclusion/exclusion criteria, number of subjects, duration of the clinical investigation, follow-up, objective(s) and endpoint(s).

NOTE It can be useful to include a flow chart showing the key stages of the clinical investigation or any other information that can be of value for the conduct of the clinical investigation.

A.2 Identification and description of the investigational device

a) Summary description of the investigational device.

b) Details concerning the manufacturer of the investigational device.

c) Name or number of the model/type, including software version and accessories, if any, to permit full identification.

d) Description as to how traceability shall be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers, or serial numbers.

e) Intended purpose of the investigational device in the proposed clinical investigation.

f) The populations and indications for which the investigational device is intended.

g) Description of the investigational device, including any materials, that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.

h) Summary of the necessary training and experience needed to use the investigational device based on risk assessment.

i) Description of the specific medical or surgical procedures involved in the use of the investigational device.

j) References to the IB and IFU.

The above information shall also be provided as far as available for the comparator, if applicable.

A.3 Justification for the design of the clinical investigation

Justification for the design of the clinical investigation, which shall be based on the conclusions of the clinical evaluation, as specified in 6.3, and shall comprise

a) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable carried out to justify the use of the investigational device in human subjects,

b) an evaluation of clinical data that are relevant to the proposed clinical investigation,

c) a description of the clinical development stage (see Annex I), if appropriate.

A.4 Benefits and risks of the investigational device, clinical procedure, and clinical investigation

a) Anticipated clinical benefits.

b) Anticipated adverse device effects (see 6.2.2).

c) Risks associated with participation in the clinical investigation (see 6.2.3).

d) Possible interactions with concomitant medical treatments as considered under the risk analysis.

e) Steps that will be taken to control or mitigate the risks.

f) Rationale for benefit-risk ratio.

A.5 Objectives and hypotheses of the clinical investigation

a) The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified.

b) Objectives, primary and secondary, described as 'superiority', 'non-inferiority', or 'equivalence', if applicable.

c) Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.

d) Primary and secondary hypotheses, if applicable.

e) Risks and anticipated adverse device effects that are to be assessed.

The objective(s) shall serve the purpose of the clinical investigation and shall relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population. The objectives of the clinical investigation shall translate directly into the pre-specification and operationalisation of the primary endpoint(s). Claims shall be linked to eligibility criteria for subject and users.

A.6 Design of the clinical investigation

A.6.1 General

a) Description of the design type of clinical investigation to be performed (e.g. randomized, blinded or open-label, parallel groups or crossover, multicentre, international) the control group, (e.g. comparative claim and reversible treatment of a chronic state) and the comparator with rationale and justification for the choice.

   Absence of control(s) shall be justified.

b) Description of the measures to be taken to minimize or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors.

c) Primary and secondary endpoints, with rationale for their selection and measurement. If applicable, composite endpoints, with rationale for their selection and measurement.

The primary endpoint shall be appropriate for the investigational device and should be clinically relevant.

NOTE Composite endpoint is a pre-specified combination of more than one endpoint and can be used cautiously by including only components that have relatively equal clinical importance, frequency, and anticipated response to the presumed mechanism of action.

d) Methods and timing for assessing, recording, and analysing variables. e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.

f) Any procedures for the replacement of subjects (generally, not applicable to randomized clinical investigations).

g) Investigation sites: number, location, and, if appropriate, differences in investigation site environment.

h) Definition of completion of the clinical investigation (see 8.1).

A.6.2 Investigational device(s) and comparator(s)

a) Description of the exposure to the investigational device(s) or comparator(s), if used.

b) List of any other medical device or medication to be used during the clinical investigation if not already specified in the instructions for use.

c) Number of investigational devices to be used, together with a justification.

A.6.3 Subjects

a) Inclusion criteria for subject selection.

b) Exclusion criteria for subject selection.

c) Criteria and procedures for subject withdrawal or lost to follow-up

1) when and how to withdraw a subject from the clinical investigation or stop the use of the investigational device,

2) documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons,

3) whether and how subjects are to be replaced.

d) Point of enrolment.

e) Point of randomization, if applicable.

f) Total expected duration of the clinical investigation.

g) Expected duration of each subject's participation.

h) Number of subjects required to be included in the clinical investigation, and where needed, anticipated distribution of enrolment among the participating investigation sites.

i) Estimated time needed to select this number (i.e. enrolment period).

j) Relationship of investigation population to target population.

k) Information on vulnerable, pregnant, and breastfeeding population, if applicable.

A.6.4 Procedures

a) Description of all the clinical investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice.

b) Description of those activities performed by sponsor representatives (excluding monitoring).

c) Any known or foreseeable factors that can compromise the outcome of the clinical investigation or the interpretation of results.

EXAMPLE Factors include subject baseline characteristics, concomitant medication, the use of other medical devices, and subject-related factors such as age, gender, or lifestyle.

d) The methods for addressing these factors in the clinical investigation, for example, by subject selection, clinical investigation design, such as stratified randomization, or by statistical analysis shall be described.

e) The follow-up period during the clinical investigation shall permit the demonstration of clinical performance, effectiveness or safety over a period of time sufficient to represent a realistic test of the investigational device and allow any risks associated with adverse device effects to be identified and assessed.

f) Address what specific medical care is appropriate to be provided for the subjects after the clinical investigation has been completed, if applicable.

g) Address recommended follow-up for the subjects after the clinical investigation has been completed.

h) Address the final disposition or potential future use of samples obtained from subjects, if applicable.

A.6.5 Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned.

It is possible to provide a detailed plan for monitoring arrangements separately from the CIP.

A.7 Statistical design and analysis

With reference to A.5 and A.6, the description of and justification for statistical design and analysis of the clinical investigation shall cover the following.

a) Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that take into account all the data.

b) Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.

c) Analytical procedures including measures of precision such as confidence intervals, if applicable.

d) The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable.

If a hypothesis is tested, a significance level alpha 0,05 (two-sided) and 0,025 (one-sided) and powers between 0,8 and 1 minus alpha need no justification. Depending on the characteristics of the investigational medical device or the clinical investigation, higher or lower levels of significance can be used. Examples of justifications include but are not limited to: product standards, scientific reasons or discussion with regulatory authorities.

e) Sample size calculation and justification taking into account:

1) all relevant clinical data on outcome variable and effect size, if applicable;

2) assumptions of expected outcomes across treatment groups, if applicable;

3) adjustments due to any pre-planned interim analyses, if applicable;

4) detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable;

5) randomization allocation ratio (e.g. 1:1, 1:2), if applicable;

6) expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).

All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided.

For exploratory and observational clinical investigations (see Annex I), in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size shall be provided.

f) The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable.

g) Pass/fail criteria to be applied to the results of the clinical investigation.

h) The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable.

i) Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof.

j) Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).

k) Description of procedures for multiplicity control and adjustment of error probabilities, if applicable.

l) The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.

m) Management, justification, and documentation of missing, unused or spurious data, including drop-outs.

n) Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable.

o) Procedures for reporting any deviation(s) from the original statistical analysis plan.

p) For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.

q) A strategy for pooling data, if applicable.

Further or more specific information can be found in standards for different types of medical devices or in national regulations or guidance documents (see References [9], [10], [13]).

A.8 Data management

a) Methods (e.g. CRF) for data entry and collection.

b) Procedures used for CRF tracking, data review, database cleaning, and issuing and resolving data queries. Specifically, timely, and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, are necessary to ensure delivery of a quality database and the achievement of the clinical investigation objectives through the implementation of the planned analysis.

c) Procedures for verification, validation, and securing of electronic clinical data systems, if applicable.

d) Procedures to maintain and protect subject privacy.

e) Methods for database locking at the start of the analysis and storage upon completion of the clinical investigation.

f) Procedures for data retention.

g) Specified retention period.

h) Other aspects of clinical quality assurance, as appropriate.

A.9 Amendments to the CIP

Description of the procedures to amend the CIP.

A.10 Deviations from clinical investigation plan

a) Statement specifying that the investigator is not allowed to deviate from the CIP, except as specified in 5.6.4 c).

b) Procedures for recording, reporting, and analysing CIP deviations.

c) Notification requirements and time frames.

d) Corrective and preventive actions and principal investigator disqualification criteria.

A.11 Device accountability

a) Description of the procedures for the accountability of investigational devices as specified in 7.9;

b) Procedures and particular materials and instructions for the safe return of investigational devices, including those that are potentially hazardous.

A.12 Statements of compliance

a) Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [7]).

b) Statement specifying compliance with this document and any regional or national regulations, as appropriate.

c) Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC and regulatory authority have been obtained, if appropriate.

d) Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

e) Statement specifying the type of insurance that shall be provided for subjects, if appropriate.

f) Statement addressing the financing of the clinical investigation including a description of the agreement between the sponsor and investigation site(s), and where applicable with the investigator(s) if not addressed in a separate agreement.

A.13 Informed consent process

a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information and process for incentives for subjects, as needed.

b) Description of the informed consent process in circumstances where the subject is unable to give it; in the case of emergency treatment, the items specified in 5.8.3.4 shall be included.

A.14 Adverse events, adverse device effects, and device deficiencies

a) Definitions of adverse events and adverse device effects.

b) Definition of device deficiencies.

c) Definitions of serious adverse events including serious health threat and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.

d) List of non-reportable adverse events, if applicable, including rationale.

e) Time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority.

f) Details of the process for reporting adverse events (date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the investigational device and the related procedure).

g) Details of the process for reporting device deficiencies.

h) List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment.

i) Emergency contact details for reporting serious adverse events and serious adverse device effects.

j) Information regarding the DMC, if established.

A.15 Vulnerable population (if applicable)

a) Description of the vulnerable population to be included in the clinical investigation.

b) Description of the screening process to identify and protect the vulnerable population.

c) Description of the specific informed consent process.

d) Description of the EC's specific responsibility.

e) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

A.16 Suspension or premature termination of the clinical investigation

a) Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.

b) Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation, if the clinical investigation involves a blinding/masking technique.

c) Requirements for subject follow-up and continued care.

A.17 Publication policy

a) Statement that the clinical investigation will be registered in a publicly accessible database (see 5.4).

b) Statement indicating that the results of the clinical investigation will be made publicly available.

c) Statement indicating the conditions and timeframes under which the results of the clinical investigation will be offered for publication including the role of the sponsor and criteria for authorship.

A.18 Bibliography

List of bibliographic references pertaining to the clinical investigation.

A.6 Appendix B from ISO 14155: 2020

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Annex B (normative)

Investigator's brochure (IB)

B.1 General

B.1.1 Introduction

If the required information of the IB is provided in other documentation (e.g. the CIP or instructions for use); such documents shall be referenced in the IB and shall be made available upon request.

The content of the IB shall contain, as a minimum, all topics listed in this annex.

NOTE Not all requirement elements might be relevant for post-market clinical investigations or information can be described in other product documentation (see I.7).

The information shall be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased benefit-risk analysis of the appropriateness of the proposed clinical investigation. For this reason, a medically qualified person shall generally participate in the editing of an IB, but the contents of the IB shall be approved by the disciplines that generated the described data.

B.1.2 Identification of the IB

a) Name of the investigational device.

b) Document reference number, if any.

c) Version or date of the IB.

d) Confidentiality statement, if appropriate.

e) Summary of the revision history in the case of amendments, if appropriate.

f) Version/issue number and reference number, if any, with the page number and the total number of pages on each page of the IB.

g) Table of contents.

B.1.3 Sponsor/manufacturer

Name and address of the sponsor of the clinical investigation and manufacturer of the investigational device, if different from the sponsor.

B.2 Investigational device information

a) Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device.

b) Statement concerning the regulatory classification of the investigational device, if relevant.

c) General description of the investigational device and its components, including any materials used, and details on those that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human, or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.

d) Summary of relevant manufacturing processes and related validation processes, to demonstrate that the investigational devices are manufactured and verified under a controlled process according to the applicable regulations.

e) Description of the mechanism of action of the investigational device, along with supporting scientific literature.

f) Manufacturer's instructions for installation, maintenance of hygienic conditions and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant.

g) Sample of the label, for example sticker or copy, and instructions for use or reference to, and information on any training required.

h) Description of the intended clinical performance.

B.3 Preclinical testing

Summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing, justifying its use in human subjects.

The summary shall include or, where applicable, refer to the results of

a) design calculations,

b) *in vitro* tests,

c) mechanical and electrical safety tests,

d) reliability tests,

e) validation of software relating to the function of the device,

f) any performance tests,

g) *ex vivo* tests,

h) *in vivo* animal test,

i) evaluation of biological safety,

j) validation of procedures for cleaning, disinfection, or sterilization.

NOTE 1 Guidance on the biological evaluation of medical devices is given in ISO 10993-1.

NOTE 2 For animal tests, include specifications of species, number of animals per group, devices used, and duration of exposure.

B.4 Existing clinical data

a) Summary of relevant previous clinical experience with the investigational device and with medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device.

b) Analysis of adverse device effects and any history of modification or recall.

B.5 Risk management of the investigational device

a) Summary of the benefit-risk analysis including identification of residual risks.

b) Contra-indications and warnings for the investigational device.

B.6 Regulatory and other references

a) List of international standards, if any, complied with in full or in part.

b) Statement of conformity with national regulations, where appropriate.

c) List of references, if relevant.

A.7 Appendix D from ISO 14155: 2020

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Annex D(normative)Clinical investigation report

D.1 General

This annex specifies the contents of the clinical investigation report that describes the design, conduct, statistical analysis, and results of a clinical investigation.

The format given in this annex may also be used in interim, progress or annual reports, if such reports are required, however some sections might only apply to the final report.

D.2 Cover page

The title page shall contain the following:

a) title of the clinical investigation;

b) if not clear from the title, a single sentence describing the design, comparison, period, usage method, and subject population;

c) identification of the investigational devices, including names and models, as relevant for complete identification;

d) name and contact details of sponsor or sponsor's representative;

e) CIP identification;

f) publicly accessible database registration number;

g) name and department of coordinating investigator and names of other relevant parties (e.g. experts, biostatistician, laboratory personnel);

h) statement indicating whether the clinical investigation was performed in accordance with this document or any other applicable guidelines and applicable regulations;

i) date of report;

j) author(s) of report.

D.3 Table of contents

The table of contents shall include the following:

a) the page number or locating information of each section, including summary tables, figures, and graphs;

b) a list of appendices and their location.

D.4 Summary

The summary shall contain the following:

a) the title of the clinical investigation;

b) an introduction;

c) the purpose of the clinical investigation;

d) the description of the clinical investigation population;

e) the clinical investigation method used;

f) the results of the clinical investigation;

g) the conclusion;

h) the date of the clinical investigation initiation;

i) the completion date of the clinical investigation or, if the clinical investigation is discontinued, the date of premature termination.

D.5 Introduction

The introduction shall contain a brief statement placing the clinical investigation in the context of the development of the investigational device and relating the critical features of the clinical investigation (e.g. objectives and hypotheses, target population, treatment and follow-up duration) to that development.

Any guidelines that were followed in the development of the CIP or any other agreements/meetings between the sponsor and regulatory authorities that are relevant to the particular clinical investigation should be identified or described.

D.6 Investigational device and methods

D.6.1 Investigational device description

The description of the investigational device shall contain the following:

a) a description of the investigational device;

b) the intended use of the investigational device(s);

c) previous intended uses or indications for use, if relevant;

d) any changes to the investigational device during the clinical investigation or any changes from the IB, including

1) raw materials,

2) software,

3) components,

4) shelf-life,

5) storage conditions,

6) instructions for use, and

7) other changes.

D.6.2 Clinical investigation plan (CIP)

A summary of the CIP, including any subsequent amendment(s) with a rationale for each amendment, shall be provided. The summary shall include a brief description of the following:

a) the clinical investigation objectives;

b) the clinical investigation design including

1) the type of clinical investigation,

2) the clinical investigation endpoints, and

3) the control group;

c) the ethical considerations;

d) the data quality assurance;

e) the subject population for the clinical investigation, with the

1) inclusion/exclusion criteria, and

2) sample size;

f) the treatment and treatment allocation schedule;

g) any concomitant medications/treatments;

h) the duration of follow-up;

i) the statistical design, analysis, and justifications including

1) the clinical investigation hypothesis or pass/fail criteria,

2) a sample size calculation,

3) statistical analysis methods,

4) interim analyses, if applicable.

D.7 Results

The results section shall include the following:

a) the clinical investigation initiation date;

b) the clinical investigation completion/suspension date;

c) the disposition of subjects; numbers screened, randomized and received therapy;

d) the disposition of investigational devices;

e) the subject demographics and other relevant baseline characteristics;

f) CIP compliance;

g) an analysis with rationale and justifications, which includes

1) all clinical performance, effectiveness or safety analyses provided for in the CIP,

NOTE These include results for the components of composite endpoints, when used.

2) a summary of all adverse events and adverse device effects, including a discussion of the severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure,

3) a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any corrective actions taken during the clinical investigation, if any,

4) any needed subgroup analyses for special populations (i.e. gender, racial/cultural/ethnic subgroups), as appropriate,

5) an accountability of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects

i) not passing screening tests,

ii) lost to follow-up, and

iii) withdrawn or discontinued from the clinical investigation and the reason.

6) clear distinctions between primary analyses, other pre-specified analyses, and additional analyses,

h) listings of deaths and reasons for deaths.

D.8 Discussion and overall conclusions

The conclusions shall be based on the intended use and target population of the investigational device and shall include the following:

a) the clinical performance, effectiveness, or safety results and any other endpoints;

b) an assessment of benefits and risks;

c) a discussion of the clinical relevance and importance of the results in the light of other existing data;

d) any specific benefits or special precautions required for individual subjects or groups considered to be at risk;

e) any implications for the conduct of future clinical investigations;

f) any limitations of the clinical investigation including but not limited to:

1) selection, retention, and compliance of subjects,

2) selection, retention, adherence (to CIP, instructions for use and the requirements of this document) of investigation sites and users, and investigation site environment type(s),

3) bias introduced by missing observations, by confounders and by 1) and 2) above.

Requirements in f) also apply to the control group(s).

D.9 Abbreviated terms and definitions

A list of abbreviated terms and definitions of specialized or unusual terms shall be provided.

D.10 Ethics

The ethics section shall include the following:

a) confirmation that the CIP and any amendments to it were reviewed by the EC (if required);

b) list of all ECs consulted (can be given in an annex; see **D.13**);

c) confirmation that the clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki;

d) statement that informed consent was obtained and when it was obtained.

D.11 Investigators and administrative structure of clinical investigation

The overview of the administrative structure shall include the following:

a) a brief description of the organization of the clinical investigation;

b) a list of investigators, including their affiliations (can be given in an annex; see D.13);

c) the names and addresses of any external organizations (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation (can be given in an annex; see D.13);

d) the names and addresses of the sponsor(s) or sponsors' representative(s).

D.12 Signature page

The signatures of the sponsor and coordinating investigator(s), indicating their agreement with the contents of the report, shall be provided. If no coordinating investigator is appointed, then the signature of the principal investigators shall be obtained. The signature pages may be separate from the clinical investigation report itself.

D.13 Annexes to the report

There can be annexes to the report which contain the following:

a) the CIP, including amendments;

b) the instructions for use;

c) the list of principal investigators and their affiliated investigation sites, including a summary of their qualifications or a copy of their CVs;

d) the list of names and addresses of any external organizations (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation;

e) the list of monitors;

f) the list of ECs;

g) the tabulation of all relevant data sets, including

1) CIP deviations that can have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation,

2) all adverse events, adverse device effects and device deficiencies, and

3) withdrawals and discontinuations,

h) the audit certificate, if applicable.

A.8 Overview of location of references of extracted recommendations of national regulators, EU and IMDRF documents

Table 40. Overview of references of extracted recommendations of all topics

Regulatory document	Level of evidence/ Description of study types	Need for CI/ Substantial equivalence	Choice of study design	Objective/ PICO	Statistical methods	Context	Reporting	References
FDA 2010 Bayes	-	-	General 2.5, 4. Bayesian 2.2,2.6, 2.7	See table PICO	2.2, 2.6-7, 4.5.-4.8, 5, 7.1	(5.6) Causes for differences in different periods of recruitment	7.1 protocol only	-
FDA 2013 Design Consid Pivotal	1., 6.,7.8, glossary	-	19, 7 24-38	See table PICO	9.3-9.4, 10	4.2, 6.4 p21 6.6 p22Glossary	10 protocol only	DH, ISO 14155:2011, ICH E6
FDA 2014 510 k Substantial Equivalence	Appendix B/	/IV.F additional investigations to proof SE	-	-	-	-	-	-
FDA 2014 Evaluation Sex-specific data	-	-	-	See table PICO	V.A (p14-16) V.B (p16-18) V.C (p18-19-20) See Appendix 1*	-	(V.C p19) VI p21ff*	-
FDA 2016 Adaptive Trial Designs	-	-	-	-	4., 9., 10.	-	CIP, SAP,11.D.	-

Regulatory document	Level of evidence/ Description of study types	Need for CI/ Substantial equivalence	Choice of study design	Objective/ PICO	Statistical methods	Context	Reporting	References
FDA 2017 Evaluating and Reporting Age, Race, ethnicity data	-	-	Refer to P in PICO see III. D IV.A (1),(2)	See table PICO	V. A refers to guidance on sex-specific data, see Appendix 1*	-	See Appendix 1 and sex-specific guidance*	-
FDA 2019a Factors Benefit Risk Determ. PMA	-	-	-	See table PICO	-	-	-	-
FDA 2019b Uncertainty in Benefit-Risk	-	-	-	-	P12 18,22 Significance level	-	(P18,21 Report post-market shift in SSED)**	-
FDA 2022 Health of Women	-	-	-	See table PICO	Priority 1 p13, 15*	-	-	-
FDA 2022 Patient Engagement	-	-	-	See table PICO	-	-	-	-
TGA 2022 Evidence requirements	p29, p66, p81, p114,137,	(p12f), p19-21, /47,**48**, 47-52	29, DS 64,66 78,81,99, 101,112, 114,135,137	See table PICO	X 29, 32, 34 DS (81) (statistical power calculation), 86 MEDDEV ref 31/32, 33	Procedure variables 85 Contextual confounders 33	23f, reference to ISO 14155 and reporting standards	ISO 14155 ISO 14971 ISO 13485: 2016 QM FDA 2019a FDA 2017 RWE Device-specific ISOs, ARC docs IMDRF MEDDEV 2.7/1 r 4

Regulatory document	Level of evidence/ Description of study types	Need for CI/ Substantial equivalence	Choice of study design	Objective/ PICO	Statistical methods	Context	Reporting	References
								MDCG 2020-5 Reporting standards
MHRA 2021 compiling a submission	-	-	-	-	-	-	CIP ISO p8f IB ISO	ISO 14155:2020 14971:2019
MHRA 2021 Clinical investigations Manufacturer	-	p5, 9. p10/ -	p 12-14	See table PICO	-	-	-	ISO 14155:2020
MHRA 2021 CI. Statistical considerations	-	-	1.4, 1.5	See table PICO	1.2, 2., 3	-	CIR 4. p11	ISO 14155:2020 ICH: GCP E6
Canada 2013 Inclusion of women	-	-	-	See table PICO	1.5 p8, 2.2 p13f, p14, 2.6 p25	-	-	ISO 14155 ICH E6
FAHMP BE 2021 CI. Guidance on dossier content	-	-	-	-	-	-	3.5 (CIP); 3.6 (IB) 3.8 (CEP) No CIR	ISO 14155
Japan 2017 Clinical Trial guidance	-	2. p3-6 3.3.2 different devices p9	3. p7-8, 4. [3] p11	See table PICO	5. p13	-	-	-
MEDDEV 2.7/1 rev 4 2016	-	Determine need of CI 10.2c;(10.3); A2	-	A3 Description of device Evaluation of benefits, risks, A7.2.b, c, d	A6b, c,d,e,f	A6	- No CIR	ISO 14155:2011 ISO 14971:2012

Regulatory document	Level of evidence/ Description of study types	Need for CI/ Substantial equivalence	Choice of study design	Objective/ PICO	Statistical methods	Context	Reporting	References
		/Equivalence A1		Appraisal of method quality 9.3.1;9.3.2;9.3., Validity A.6				
MDCG 2019-9 rev. 1 SSCP	-	-	-	-	-	-	/5.2 p16 Reporting CI in SSCP	MDR
2020-6 clinical evidence legacy devices	-	Def. well-established technol. under the MDR p5 "similar device" p6 equivalence defined in MDR (Annex XIV, Part A, sec 3 6.5e lack of sufficient data legacy devices	-	Refers to MEDDEV 2.7/1 Rev. 4 A.3 still valid 6.1c benefits and outcome parameters refers to MEDDEV A7.2 section b and c (6.1d proposed level of clinical evidence MEDDEV A6, 9.3.2) 6.5 Analysis of clinical data, a) benefits refers to MEDDEV A7.2 b), c)	-	-	-	MEDDEV 2.7/1 rev 4 2016 MDR IMDRF WG/N47

Regulatory document	Level of evidence/ Description of study types	Need for CI/ Substantial equivalence	Choice of study design	Objective/ PICO	Statistical methods	Context	Reporting	References
				6.5b risks refers to MEDDEV A7				
MDCG 2020-5 equivalence	-	Equivalence Points out differences between MDR and MEDDEV 2.7/1 Rev. 4	-	-	-	-	-	MEDDEV 2.7/1 r 4 2016 MDR
MDCG 2020-10 Safety reporting in CI	-	-	-	O: 3. definition of AE p5 9. causality assessment	-	-	4.Reporting methods AE (template) 5. Reportable events 10. Reporting form	MDR
MDCG 2020-13 CEAR template	-	-	-	-	-	-	Section E Clinical investigations	MDR
MDCG 2021-06 Q&A CI	-	-	-	Def. performance, clinical performance, benefit p6	-	-	11. AE reporting ref to MDCG 2020-10 24. CIR within 1 year CIR: Reference to MDR chapter III point 7 of Annex XV and	MDR MDCG 2020-10/1

Regulatory document	Level of evidence/ Description of study types	Need for CI/ Substantial equivalence	Choice of study design	Objective/ PICO	Statistical methods	Context	Reporting	References
							ISO 14155 Annex D additional information see 25.p15	
MDCG 2021-08 CI application	Annex 1 2.2-2.4,4.	-	-	-	-	-	-	MDR
IMDRF 2019 CI	-	2.0 scope therapeutic devices for marketing authorization 5.0 When should a CI be undertaken, clarifying need for CI	6.0	Def. objective p4, 6.0 Conduct ISO14155	6.0 statistical plan	6.0 learning curves	6.0 CIP p9	Several GHTF and IMDRF docs ISO 14155:2011, 14971: 2007
IMDRF 2019 CEval	-	-	-	-	-	-	-	Several GHTF and IMDRF docs ISO 14155:2011, 14971: 2007
IMDRF 2020 AE reporting	-	-	-	(AE)	-	-	AE	-

* Reported under subgroup analysis in section “Statistical Methods”, ** not mentioned in text.

AE: adverse event, CI: clinical investigation, CIP: clinical investigation plan, CIR: clinical investigation report, Def.: Definition, DS: device-specific DH: declaration of Helsinki, FDA: U. S. Food and Drug Administration, GHTF: Global Harmonization Task Force, IB: Investigator’s brochure, IMDRF: International Medical Device Regulators Forum, ISO:

International Organization for Standardization, MDCG: Medical Device Coordination Group, MDR: Medical Device Regulation, SSCP: summary of safety and clinical performance, WG: working group.

Table 41. Overview of references of extracted recommendations of "Objectives/ PICO" part

Regulatory document	Objective	Population	Intervention	Comparator	Outcomes	Validity
FDA 2010 Bayes	4.2 inference to target population	4.1 as issue in protocol and 4.3 collection of covariates 3.7 Exchangeability of study patients with target population	-	4.4	4.2 endpoints	-
FDA 2013 Design Consid Pivotal	6.3 definition, role study objective	6.4 Representativeness vulnerable populations Selection method 6.5 stratification 6.6 site selection	10. protocol, description of treatment and test procedures	6.7 descriptive and recommendations 7.4 see table 1 Table 1 check what was used 7.6 OPC, OG	7.1	6.2 Bias and Variability 7.2 Intervention assignment 7.3 blinding 7.5 placebo effect 7.6.1-3 7.8 refer to levels of evidence Refer to section level of evidence
FDA 2014 510 k Substantial Equivalence	-	-	Annex B Description of device	-	-	-
FDA 2014 Evaluation Sex-specific data	-	Promote appropriate enrolment of women see IV.B.1.a.-j	-	-	-	-

Regulatory document	Objective	Population	Intervention	Comparator	Outcomes	Validity
FDA 2016 Adaptive Trial Designs	-	-	-	-	-	- see statistical methods
FDA 2017 Evaluating and Reporting Age, Race, ethnicity data	Appendix 1 p32 Look for group differences in scientific data Pre-specification subgroup reporting/ analyses IV.A.	III.B. Terminology (III.D.1, D.2 Recruit diverse populations Barriers, resources enrolment) IV.B.1 a-i recommendations enrolment	-	-	-	-
FDA 2019a Factors Benefit Risk Determ. PMA	-	-	-	-	IV. A. B.	-
FDA 2019b Uncertainty in Benefit-Risk Determ.	-	-	-	-	-	-
FDA 2022 Health of Women	Subgroup-specific analyses	Priority 1 p13/p14/15 P9 collecting, analysing, reporting data in a sex-/gender-disaggreg. manner clinical trial enrolment P21	-	-	-	-
FDA 2022 Patient Engagement	-	V.A. Recruitment: informed consent, barriers options FU	-	-	V.A. Meaningful endpoints, which PRO	-

Regulatory document	Objective	Population	Intervention	Comparator	Outcomes	Validity
		visits, data collection				
TGA 2022 Evidence requirements	General – DS: joints – DS: CV -	General – IMDRF sample appraisal criteria DS: joints – DS: CV Exclusion/ inclusion criteria	-	General Clinical evaluation p28 Single arm studies inadequate evidence.	Clinical evaluation: p30 DS: Joints p64f Detailed rec p 70ff revision rates bench-marking registry data MCID p85 DS: CV p78 tables of SR for different classes of devices p84-95 coronary stents: use standardized endpoints from ARC 2007 (Cutlip)	Appraisal tools validity p 29 DS joints p82. CV p95, heart valves 129, outcome assessment blinded, independently adjudicated
MHRA 2021 compiling a submission	-	-	IB (p9)	-	-	-
MHRA 2021 Clinical investigations Manufacturer	-	-	-	-	Endpoints p13 AE p20/21 Definition Glossary AE p26	-
MHRA 2021 Cl. Statistical considerations	1.1 elaborated definition	1.3, 1.6, 1.7, 3.1	-	1.4	1.1, 1.6, 5	1.5
Health Canada 2013 Inclusion of women	Pre-specified subgroup analyses p13/14 2.6	1.3 p4-6, p9,11f Pregnancy prevention p16f	-	-	-	-

Regulatory document	Objective	Population	Intervention	Comparator	Outcomes	Validity
		Pregnant and breastfeeding women p 20ff Appendix A contraceptives p28				
FAHMP BE 2021 CI. Guidance on dossier content	-	-	CIP 3.5.2 IB 3.6.2 ISO 14155	-	-	-
Japan 2017 Clinical Trial guidance	-	- see section need for CI / population comparable to Japanese pop	-	3.1 Basic concepts on clinical trial design, appropriate control group, randomization, blinding. p7	3.1 primary endpoint use surrogate endpoint P7/8 3.3 duration follow-up P8	5 GCP trials and quality control a 5.3. Appropriate randomization,
MEDDEV 2.7/1 Rev. 4 2016*	-	9.3.1	A3 Description of device	A6d	Evaluation of benefits, risks, A7.2.b, c, d	Appraisal of methodological quality 9.3.1;(A6)
MDCG 2019-9 rev. 1 SSCP	-	-	-	-	-	-
2020-6 clinical evidence legacy devices	-	-	-	-	6.1c benefits and outcome parameters refers to MEDDEV 2.7/1 Rev 4 Appendix A7.2 section b and c 6.5 Analysis of clinical data, a)	Definition of validity

Regulatory document	Objective	Population	Intervention	Comparator	Outcomes	Validity
					benefits refers to MEDDEV A7.2 b, c 6.5b risks reference to MEDDEV A7.2d	
MDCG 2020-5 equivalence	-	-	-	-	-	-
MDCG 2020-10 Safety reporting in CI	-	-	-	-	O: 3. definition of AE p5 9. causality assessment	-
MDCG 2020-13 CEAR template	-	-	-	-	-	-
MDCG 2021-06 Q&A CI	-	-	-	-	3.Def performance, clinical performance, benefit 11. Safety reporting	-
MDCG 2021-08 CI application	-	-	-	-	-	-
IMDRF 2019 CI	-	-	-	-	-	-
IMDRF 2019 Clinical Eval	-	-	-	-	-	-
IMDRF 2020 AE reporting	-	-	-	-	AE -> reporting	-

AE: adverse event, CI: clinical investigation, CIP: clinical investigation plan, CIR: clinical investigation report Def.: Definition, DS: device-specific, DH: declaration of Helsinki, IB: Investigator's brochure, MDR: Medical Device Regulation, SAP: statistical analysis plan, SSCP: summary of safety and clinical performance.

Table 42. Overview of references of extracted recommendations of "Statistical Methods"

	Uncertainty, sample size, pre-specification, validity	Subgroup analysis	Bayesian statistics	Adaptive design
FDA 2010 Bayes	-	-	2.2, 2.6-7, 4.5.-4.8, 5, 7.1	
FDA 2013 Design Pivotal Stud.	9.3-9.4, 10	For stratified subject selection see P in PICO	-	-
FDA 2014 Evaluation Sex-specific data	-	V.A (p14-16) V.B (p16-18) V.C (p18-19-20) See Appendix 1	-	-
FDA 2016 Adaptive Trial Designs	-		6.c	4., 9., 10.
FDA 2016 Collection Race and Ethnicity data	-	IV	-	-
FDA 2017 Evaluating and Reporting Age, Race, ethnicity data	-	V. A reference to guidance on sex-specific data See Appendix 1	-	-
FDA 2019b Uncertainty in Benefit-Risk Determination	p12 18,22 Significance level, uncertainty	-	-	-
FDA 2022 Health of Women	-	Priority 1 p13, 15	-	-
TGA 2022 Evidence requirements	SSC: 29, 32, 34 DS (81) (statistical power calculation), 86 MEDDEV ref 31/32, 33	-	-	-
MHRA 2021 CI. Statistical considerations	SSC:1.2 Uncertainty, pre-specification,2.1 MISS 2.2, 2.3	-	-	3.2
Canada 2013 Inclusion of women	-	1.5 p8, 2.2 p13f, p14, 2.6 p25	-	-
Japan 2017 Clinical Trial guidance	5. p13	-	-	-
MEDDEV 2.7/1 Rev. 4	A6 b, c, f	-	-	-
IMDRF 2019 CI	6.0 Statistical plan	-	-	-

DS: device-specific, p: page PS: pre-specification, SS: sample size calculation, MISS: missing values.

A.9 Figures from Appendix 1 in the FDA guidance on evaluation and reporting of age-, race- and ethnicity-specific data in medical device clinical studies (24)

Figure 1: Recommendations for Demographic Subgroup-Specific Statistical Study Design

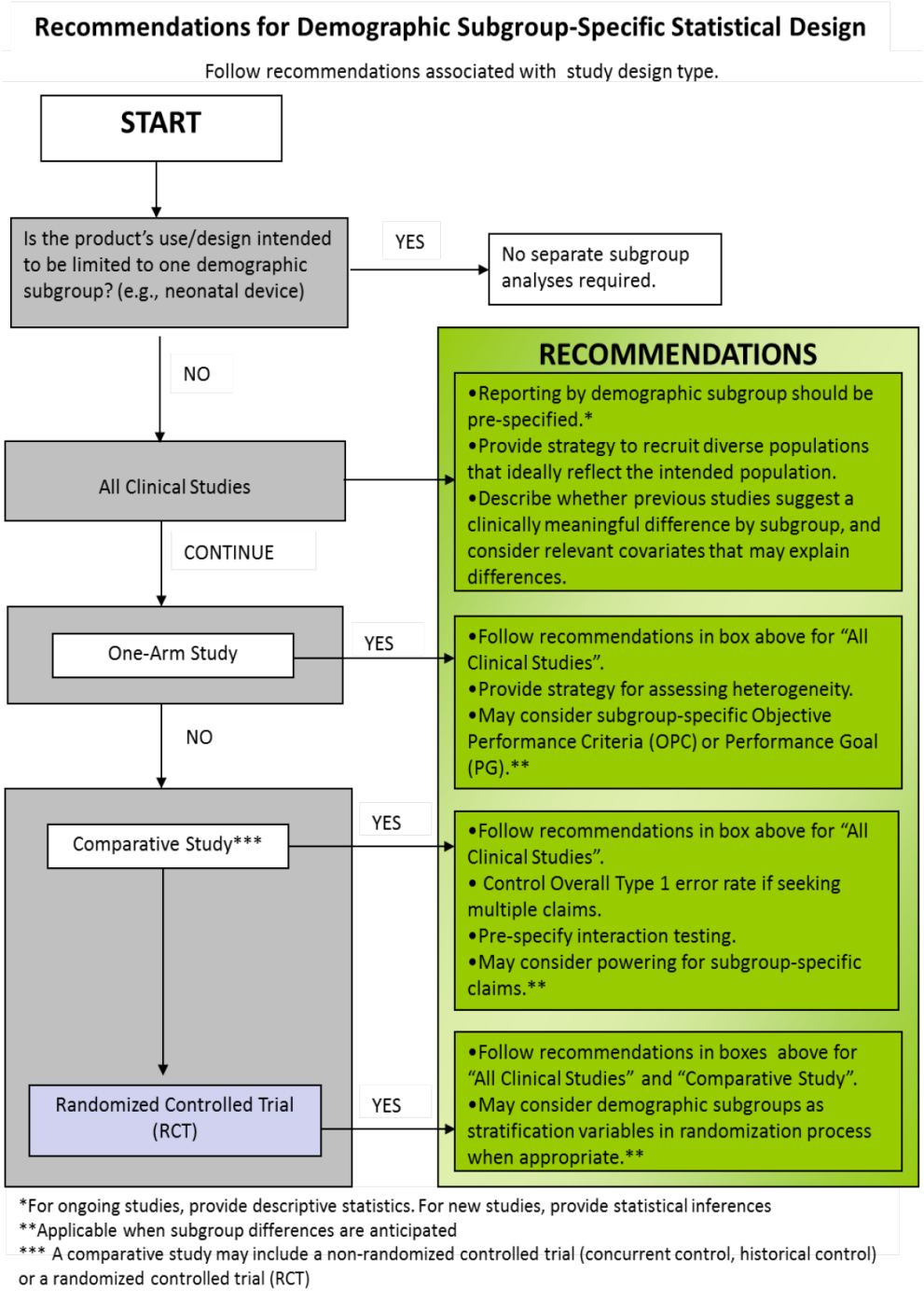
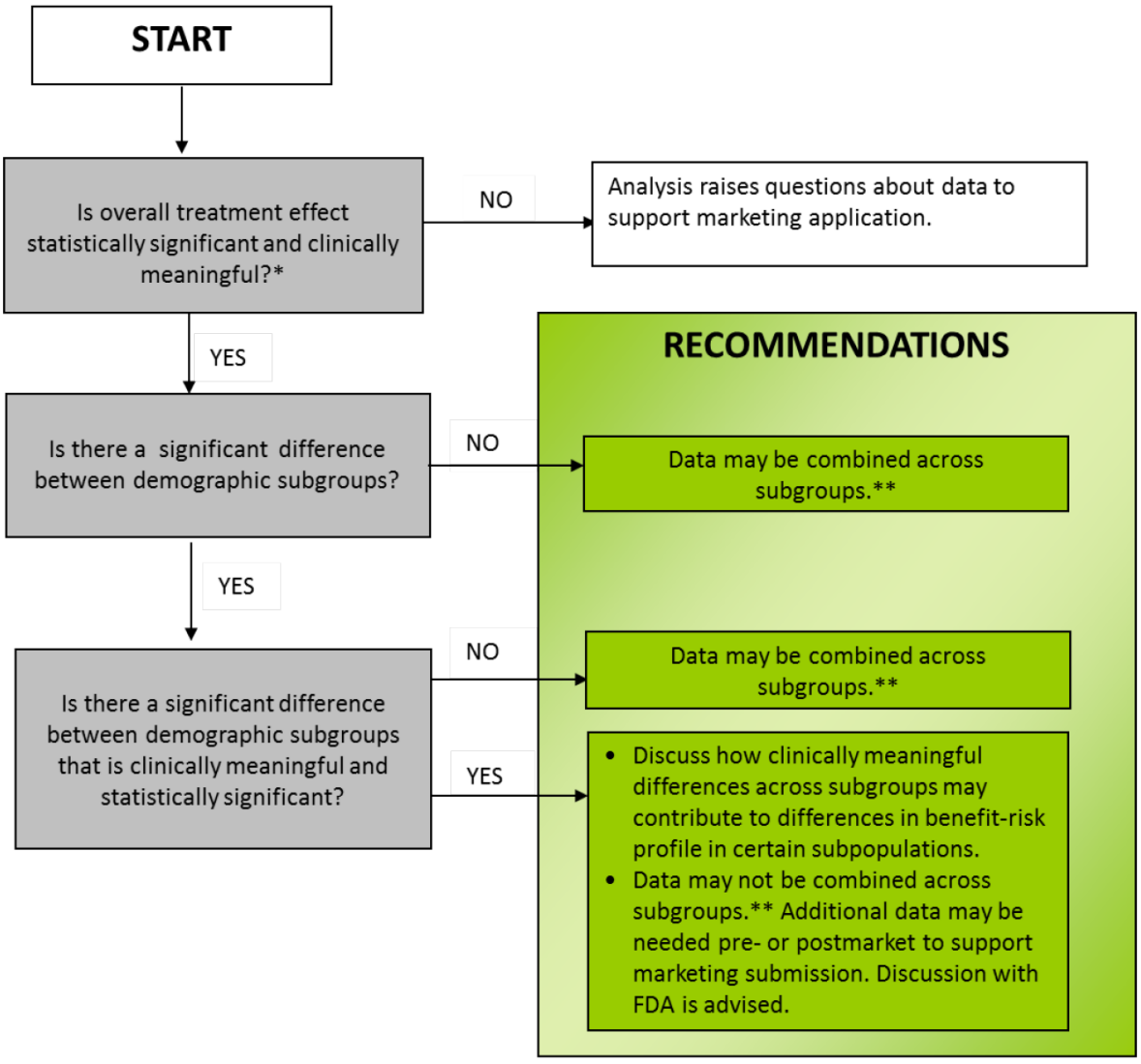


Figure 2: Recommendations for Demographic Subgroup-Specific Statistical Analysis for One-Arm Studies (Objective Performance Criterion, Performance Goal, Observational Study)

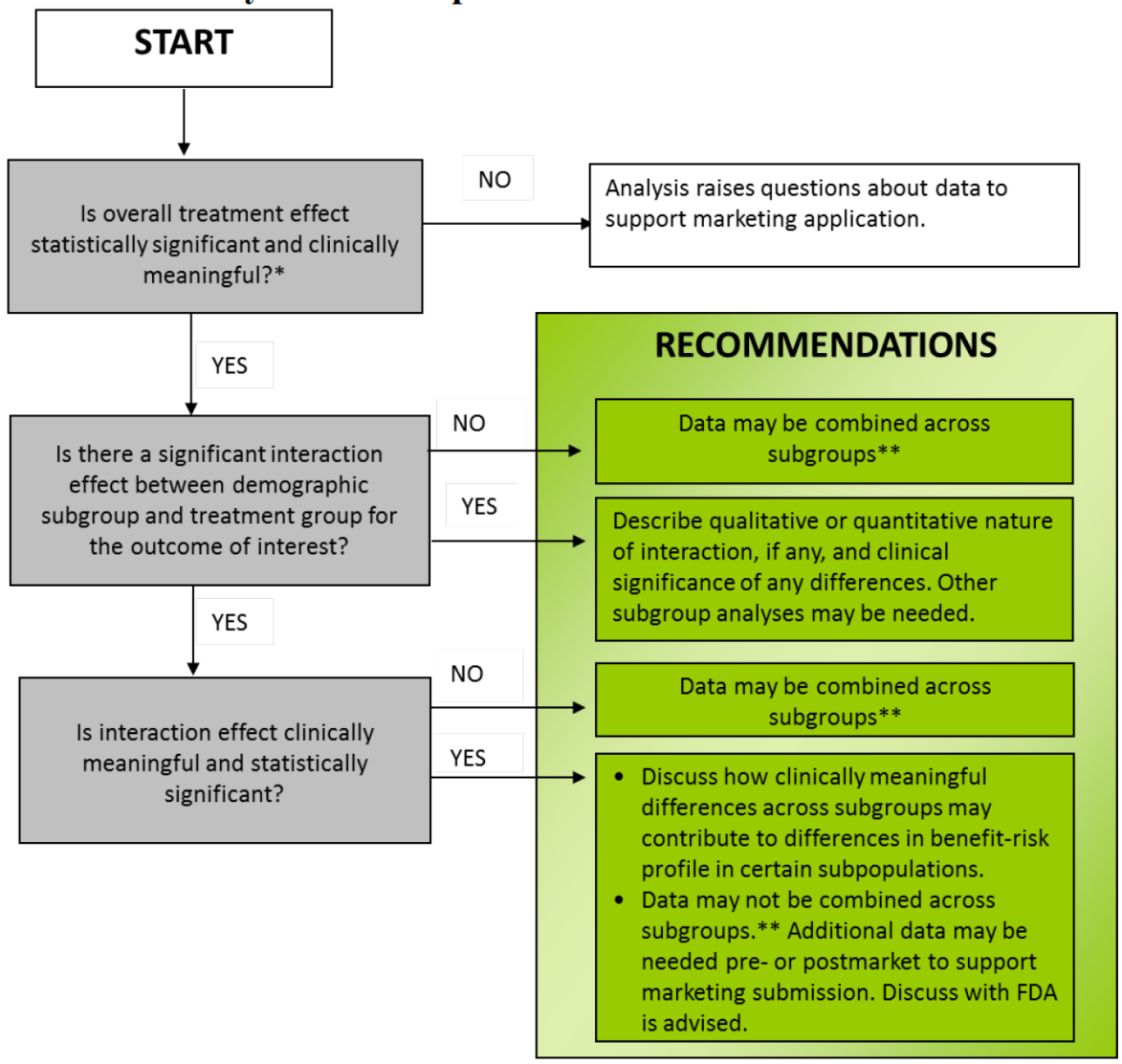


*Unplanned subgroup analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device if overall treatment effect is not statistically significant and clinically meaningful.

**Provide justification for combining data across subgroups, if applicable.

Note: In some cases, the subgroup-specific difference can be 1) statistically significant but not clinically meaningful or 2) clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.

Figure 3: Recommendations for Demographic Subgroup-Specific Statistical Analysis for Comparative Studies

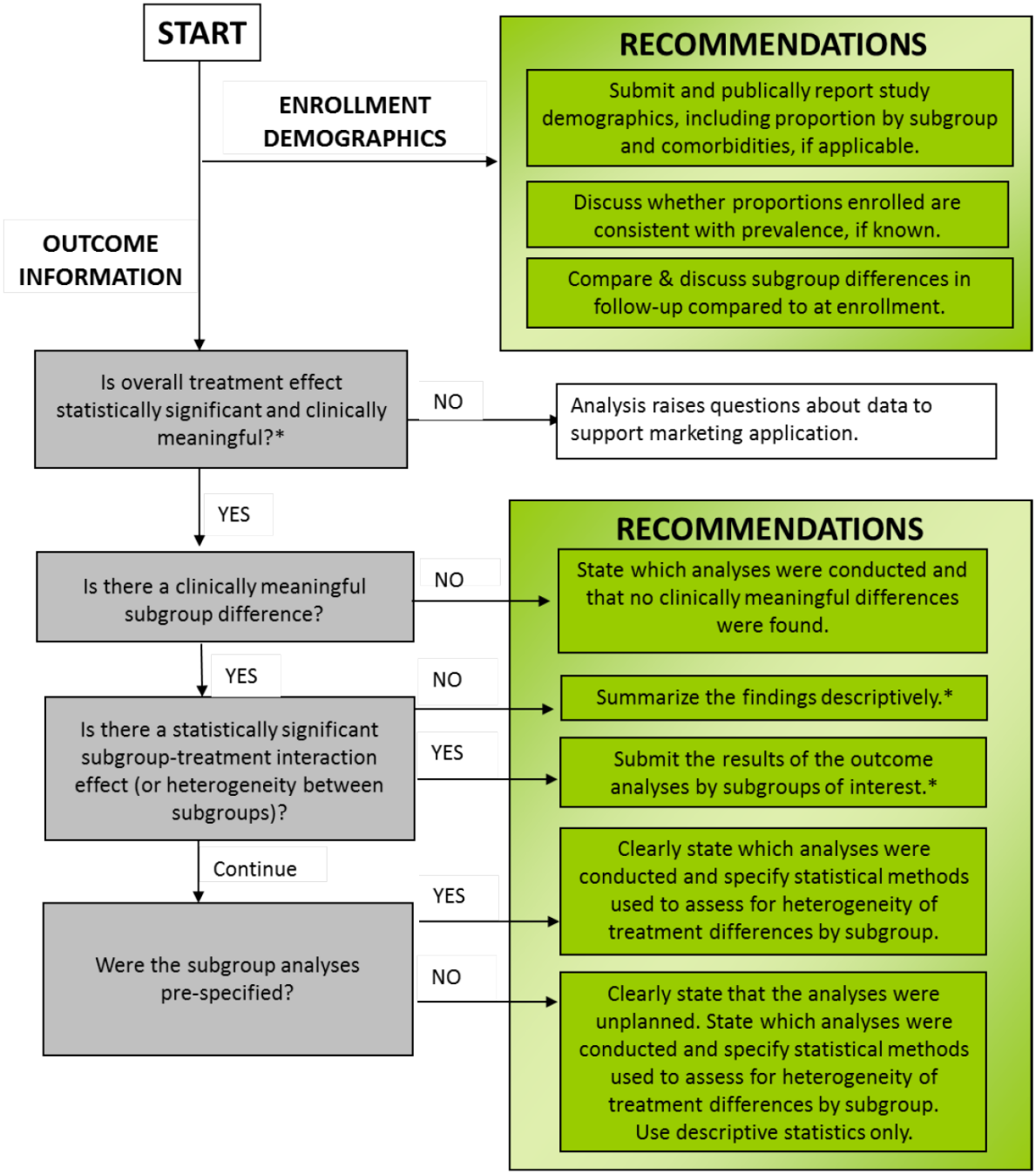


*Unplanned subgroup analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device if overall treatment effect is not statistically significant and clinically meaningful.

**Provide justification for combining data across subgroups, if applicable.

Note: In some cases, the subgroup-specific difference can be 1) statistically significant but not clinically meaningful or 2) clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.

Figure 4: Recommendations for Submitting and Reporting Subgroup-Specific Participation and Outcome Information



* Discuss how clinically meaning differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.

Note: The term "submit" refers to information submitted to the FDA for analysis. The term "report" refers to information that should be included in publically available documents (e.g., labeling, SSED).

A.10 Description of the Device, Items from Regulatory Documents of FDA, MHRA, EU, FAMHP

FDA 2104, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]. Annex B. The 510(k) Summary Document Requirements p26-30

807.92(a)(2): "The name of the device, including the trade or proprietary name if applicable, the common or usual name, and the classification name, if known."

o FDA recommends that the manufacturer list all applicable names and model numbers, if known.

o If the submission is bundled, the 510(k) Summary should list all applicable classification regulations and product codes.

807.92(a)(3): "An identification of the legally marketed device to which the submitter claims equivalence. A legally marketed device to which a new device may be compared for a determination regarding substantial equivalence is a device that was legally marketed prior to May 28, 1976, or a device which has been reclassified from class III to class II or I (the predicate), or a device which has been found to be substantially equivalent through the 510(k) premarket notification process."

o FDA recommends that the manufacturer provide the 510(k) number of the device used as the predicate device in support of the current 510(k) submission.

o If using an exempt device as a predicate, the manufacturer should list the classification regulation and the product code.

o If using a device that has been reclassified from Class III to II as a predicate, where a 510(k) has not been submitted, please list the PMA number.

o If the manufacturer lists an inappropriate predicate device, FDA will request that such information be removed and the 510(k) Summary updated accordingly by the manufacturer.

807.92(a)(4): "A description of the device that is the subject of the premarket notification submission, such as might be found in the labeling or promotional material for the device, including an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material used, and physical properties."

The description of the device attributes should include the following details:

o Device Identification:

List all key device components included in the submission (e.g., catheter, cable wire, leads)

List all model numbers (if known) and briefly explain the differences among models

o Device Characteristics (address all that apply):

software

biologics

drugs

any patient-contacting materials

coatings

additives

single-use

sterile

sterilization method [specify]

o Environment of Use (address all that apply):

healthcare facility/hospital

home

other [specify]

o Brief Written Description of the Device:

Explanation of how the device works/principle of operation

Mechanism of action

Any necessary feature to determine SE or device performance

Energy source (if applicable)

o Materials of Use

General type of material used (e.g., polysulfone, stainless steel)

If material conforms to an FDA recognized consensus standard for medical use, include the applicable number (e.g., ASTM FXXXX-last 2 numbers of the year)

Duration and type of contact

o Key Performance Specifications/Characteristics of the Device

807.92(a)(5): "A statement of the intended use of the device that is the subject of the premarket notification submission, including a general description of the diseases or conditions that the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is intended. If the indication statements are different from those of the legally marketed device identified in paragraph (a)(3) of this section, the 510(k) summary shall contain an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and why the differences do not affect the safety and effectiveness of the device when used as labeled."

o The 510(k) Summary should include the Indications for Use, which should be identical to that proposed on the Indications for Use Sheet and the labeling.

o If the Indications for Use are different from those of the predicate device, a brief explanation is required to address why the differences in the Indications do not affect the safety and effectiveness of the device and do not alter the intended therapeutic, diagnostic, prosthetic, or surgical use of the device.

807.92(a)(6): “If the device has the same technological characteristics (i.e., design, material, chemical composition, energy source) as the predicate device identified in paragraph (a)(3) of this section, a summary of the technological characteristics of the new device in comparison to those of the predicate device. If the device has different technological characteristics from the predicate device, a summary of how the technological characteristics of the device compare to a legally marketed device identified in paragraph (a)(3) of this section.”

MHRA 2021, Clinical investigations of medical devices – compiling a submission to MHRA p.9-11

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3. Clinical Investigator's Brochure

A copy of the investigator's brochure must be provided, which should be in line with

ISO14155:2020.

The following information should either be included in the Investigator's Brochure or within other documents submitted to MHRA

 Reference to important relevant scientific literature (if any) with an analysis and bibliography

 Classification of device with rationale.

 Brief description of device and its intended use together with other devices designed to be

used in combination with it.

 Design drawings, diagrams of operation and diagrams of components, sub-assemblies, circuits etc., including descriptions and explanations necessary to understand the aforementioned

drawings/diagrams.

 Photograph (preferably in colour).

 Details of any comparable device on the market

 Identification of any features of design that are different from a previously similar marketed

product (if relevant).

 Details of any new or previously untested features of the device including where applicable,

function and principles of operation.

 Summary of experience with any similar devices manufactured by the company including

length of time on the market and a review of performance related complaints.

 Summary of the risk benefit analysis to include identification of hazards and estimated risks

associated with the manufacture (including factors relating to device design, choice of

materials, software) and the use of the device (ISO 14971:2019), together with a description of what actions have been taken to minimise or eliminate the identified risk.

 Description of materials coming into contact with the body, why such materials have been

chosen, and which standards apply (if relevant).

 Identification of any special manufacturing conditions required and if so how such requirements have been met.

 A description of the methods of manufacturer, in particular as regards sterilisation and identification of packaging used for sterilisation of device.

 A summary of the relevant standards applied in full or in part, and where standards have not been applied, descriptions of the solutions adopted to satisfy the essential requirements or general safety and performance requirements.

 The results of the design calculations and of the inspections and technical tests carried out, etc.

 What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use? Including procedures for analysis of implantable devices following explant.

 Identification of any tissues of animal origin

 Identification of a substance (medicinal product), human blood derivative or non-viable human tissues and cells incorporated with the device as an integral part.

 Details of training for users (both healthcare professionals and patients)

7. Device details

The depth of detailed information supplied with the notification should be appropriate to the classification of the device, novelty of design, materials used and risks associated with the device.

 Detailed description of device, how the device is assembled and how the constituent parts are joined together

 A list of accessories, principles of operation and block or flow diagram of major components.

 Principal design drawings and circuit diagrams, together with a description and explanations necessary for the understanding of the said drawings and diagrams.

 A picture or schematic illustration of the device operation and photos of the device.

 A video demonstrating the operation of the device if available.

 For device systems provide a summary of how compatibility of all device components (whether UKCA/CE UKNI/CE marked or not) has been determined, including an updated risk analysis covering this.

 For UKCA/CE UKNI/CE marked devices being used for a new intended purpose that is not covered by the existing UKCA/CE UKNI/CE marking please provide full details of the new intended use and how this compares to the original intended use.-

 For UKCA/CE UKNI/CE marked devices being used as ‘ancillary’ devices within the study:

- Ensure the devices are being used in accordance with the UKCA/CE UKNI/CE marked

instructions for use;

- Provide evidence that the safety profile of such devices has been assessed to ensure there are no current safety concerns. This assessment should, as a basic step, involve a search of any safety notices published by the manufacturer or MHRA.

MEDDEV 2.7/1 Revision 4, 2016 Clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC Appendix A.3 p35-36

A3. Device description - typical contents

The description should be detailed enough to allow for a valid evaluation of the state of compliance with Essential Requirements, the retrieval of meaningful literature data and, if applicable, the assessment of equivalence to other devices described in the scientific literature:

• name, models, sizes, components of the device, including software and accessories

• device group to which the device belongs (e.g. biological artificial aortic valve)

• whether the device is being developed/ undergoing initial CE-marking/ is CE-marked

• whether the device is currently on the market in Europe or in other countries, since when, number of devices placed on the market

• intended purpose of the device

- exact medical indications (if applicable)

- name of disease or condition/ clinical form, stage, severity/ symptoms or aspects to be treated, managed or diagnosed

- patient populations (adults / children / infants, other aspects)

- intended user (use by health care professional / lay person)

- organs / parts of the body / tissues or body fluids contacted by the device

- duration of use or contact with the body

- repeat applications, including any restrictions as to the number or duration of reapplications

- contact with mucosal membranes/ invasiveness/ implantation

- contraindications

- precautions required by the manufacturer

- single use / reusable

- other aspects

• general description of the medical device including

- a concise physical and chemical description

- the technical specifications, mechanical characteristics

- sterility

- radioactivity

- how the device achieves its intended purpose
- principles of operation
- materials used in the device with focus on materials coming in contact (directly or indirectly) with the patient/ user, description of body parts concerned
- whether it incorporates a medicinal substance (already on the market or new), animal tissues, or blood components, the purpose of the component
- other aspects

• whether the device is intended to cover medical needs that are otherwise unmet/ if there are medical alternatives to the device / if the device is equivalent to an existing device, with a description of the situation and any new features

• if the device is intended to enter the market based on equivalence:

- name, models, sizes, settings components of the device presumed to be equivalent, including software and accessories
- whether equivalence has already been demonstrated

• Intended performance, including the technical performance of the device intended by the manufacturer, the intended clinical benefits, claims regarding clinical performance and clinical safety that the manufacturer intends to use

• For devices based on predecessor devices: Name, models, sizes of the predecessor device, whether the predecessor device is still on the market, description of the modifications, date of the modifications.

• The current version number or date of the information materials supplied by the manufacturer (label, IFU, available promotional materials and accompanying documents possibly foreseen by the manufacturer).

FAMHP 2021, Clinical Investigations. Guidance on Dossier Content. Version 2.0 p10-11; 17-18

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3.5.2. Identification and description of the investigational device

This section should include the information listed below, if applicable. If appropriate, references to the IB and/or IFU can be made. In case a comparator device is used the information below should also be provided for the comparator.

- Summary description of the investigational device.

- Details concerning the manufacturer of the investigational device.

- Name or number of the model/type, including software version and accessories to permit full identification.

- Description as to how traceability will be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers or serial numbers.

- Intended purpose of the investigational device in the clinical investigation.

- The populations and indications for which the investigational device is intended.

- A detailed description of the investigational device, including a list of all materials which will be in contact with tissues or body fluids. Also any medicinal substances, human or animal tissues or their derivates, or other biological active substances incorporated in the device must be defined.

- Summary of the necessary training and experience needed to use the investigational device based on risk assessment.

- Description of the specific medical or surgical procedures involved in the use of the investigational device. […]

3.6. Investigator's Brochure (IB)

The IB is a compilation of the current clinical and non-clinical information on the investigational medical device relevant to the clinical investigation. It also provides a benefit/risk assessment for the intended purpose of the device in the study. The content is technical and scientific. The full details of the content are provided in annex B of ISO 14155, a summary is given below.

Note that it is preferred for all necessary information to be included in the IB. However, if it is

decided to move part of the information to annexes (or other referenced documents), then a clear reference should be made in the IB and the respective documents must be submitted together with the IB as part of the initial data package accompanying the clinical investigation application.

3.6.1. General introduction

The first page(s) should contain a proper identification of the IB with the name of the investigational device, a document reference number, version or date of the IB, if appropriate a confidentiality statement, a summary of the revision history and table of contents.

The name and address of the sponsor of the clinical investigation should be given, and of the

manufacturer of the investigational device, if different from the sponsor.

3.6.2. Investigational device information

In this section detailed information is given concerning the investigational device, it must contain following elements, if applicable:

- Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device.

- Statement concerning the regulatory classification of the investigational device including a

justification based on the classification rules. The classification rules can be found in Annex

VIII of the MDR.

- A detailed description of the investigational device and its components. A clear overview of

materials used in the device should be provided. For more complicated devices, this can be accompanied by an annotated drawing or photograph of the device. Especially for all human (patient, clinician, …) contacting materials, sufficient detail should be provided, even if contact is only brief or occasional. The information provided should be sufficiently specific and should include the supplier, supplier product code, generic name, brand name and if applicable, the grade, quality, specification or standard adhered to. Preferably, the information is provided in a tabular format.

Details of any medicinal substances, human, or animal tissues or their derivates, or other biologically active substances must also be included.

- Summary of relevant manufacturing processes and related validation processes, to demonstrate that the investigational devices are manufactured and verified under a controlled process according to the applicable regulations. This can be done by means of a manufacturing flowchart. In-process controls should be described and acceptance criteria for these tests should be clearly defined.

- Description of the mechanism of action of the investigational device, along with supporting

scientific literature.

- Manufacturer's instructions for installation, maintenance of hygienic conditions and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant.

- Reference to the examples of investigational device labelling (see section3.13) and instructions for use (see section3.7). Information on any specific training, if required,

should be given here.

- Description of the intended clinical performance.

- An overview of the design history of the medical device (e.g. in table form) is recommended and appreciated. This overview should specifically focus on the devices used clinically and in confirmatory preclinical testing. Preferably, this table contains for each iteration the version number, a photograph/drawing and a brief overview and rationale of changes with regards to the previous iteration.

A.11 MDR Annex XV

ANNEX XV

CLINICAL INVESTIGATIONS

CHAPTER I

GENERAL REQUIREMENTS

1. Ethical principles

Each step in the clinical investigation, from the initial consideration of the need for and justification of the study to the publication of the results, shall be carried out in accordance with recognised ethical principles.

2. Methods

2.1. Clinical investigations shall be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims regarding the safety, performance and aspects relating to benefit-risk of devices as referred to in Article 62(1); the clinical investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions. The rationale for the design and chosen statistical methodology shall be presented as further described in Section 3.6 of Chapter II of this Annex.

2.2. The procedures used to perform the clinical investigation shall be appropriate to the device under investigation.

2.3. The research methodologies used to perform the clinical investigation shall be appropriate to the device under investigation.

2.4. Clinical investigations shall be performed in accordance with the clinical investigation plan by a sufficient number of intended users and in a clinical environment that is representative of the intended normal conditions of use of the device in the target patient population. Clinical investigations shall be in line with the clinical evaluation plan as referred to in Part A of Annex XIV.

2.5. All the appropriate technical and functional features of the device, in particular those involving safety and performance, and their expected clinical outcomes shall be appropriately addressed in the investigational design. A list of the technical and functional features of the device and the related expected clinical outcomes shall be provided.

2.6. The endpoints of the clinical investigation shall address the intended purpose, clinical benefits, performance and safety of the device. The endpoints shall be determined and assessed using scientifically valid methodologies. The primary endpoint shall be appropriate to the device and clinically relevant.

2.7. Investigators shall have access to the technical and clinical data regarding the device. Personnel involved in the conduct of an investigation shall be adequately instructed and trained in the proper use of the investigational device, and as regards the clinical investigation plan and good clinical practice. This training shall be verified and where necessary arranged by the sponsor and documented appropriately.

2.8. The clinical investigation report, signed by the investigator, shall contain a critical evaluation of all the data collected during the clinical investigation, and shall include any negative findings.

CHAPTER II

DOCUMENTATION REGARDING THE APPLICATION FOR CLINICAL INVESTIGATION

For investigational devices covered by Article 62, the sponsor shall draw up and submit the application in accordance with Article 70 accompanied by the following documents:

1. Application form

The application form shall be duly filled in, containing information regarding:

1.1. name, address and contact details of the sponsor and, if applicable, name, address and contact details of its contact person or legal representative in accordance with Article 62(2) established in the Union;

1.2. if different from those in Section 1.1, name, address and contact details of the manufacturer of the device intended for clinical investigation and, if applicable, of its authorised representative;

1.3. title of the clinical investigation;

1.4. status of the clinical investigation application (i.e. first submission, resubmission, significant amendment);

1.5. details and/or reference to the clinical evaluation plan;

1.6. If the application is a resubmission with regard to a device for which an application has been already submitted, the date or dates and reference number or numbers of the earlier application or in the case of significant amendment, reference to the original application. The sponsor shall identify all of the changes from the previous application together with a rationale for those changes, in particular, whether any changes have been made to address conclusions of previous competent authority or ethics committee reviews;

1.7. if the application is submitted in parallel with an application for a clinical trial in accordance with Regulation (EU) No 536/2014, reference to the official registration number of the clinical trial;

1.8. identification of the Member States and third countries in which the clinical investigation is to be conducted as part of a multicentre or multinational study at the time of application;

1.9. a brief description of the investigational device, its classification and other information necessary for the identification of the device and device type;

1.10. information as to whether the device incorporates a medicinal substance, including a human blood or plasma derivative or whether it is manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives;

1.11. summary of the clinical investigation plan including the objective or objectives of the clinical investigation, the number and gender of subjects, criteria for subject selection, whether there are subjects under 18 years of age, design of the investigation such as controlled and/or randomised studies, planned dates of commencement and of completion of the clinical investigation;

1.12. if applicable, information regarding a comparator device, its classification and other information necessary for the identification of the comparator device;

1.13. evidence from the sponsor that the clinical investigator and the investigational site are capable of conducting the clinical investigation in accordance with the clinical investigation plan;

1.14. details of the anticipated start date and duration of the investigation;

1.15. details to identify the notified body, if already involved at the stage of application for a clinical investigation;

1.16. confirmation that the sponsor is aware that the competent authority may contact the ethics committee that is assessing or has assessed the application; and

1.17. the statement referred to in Section 4.1.

2. Investigator's Brochure

The investigator's brochure (IB) shall contain the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application. Any updates to the IB or other relevant information that is newly available shall be brought to the attention of the investigators in a timely manner. The IB shall be clearly identified and contain in particular the following information:

2.1. Identification and description of the device, including information on the intended purpose, the risk classifi- cation and applicable classification rule pursuant to Annex VIII, design and manufacturing of the device and reference to previous and similar generations of the device.

2.2. Manufacturer's instructions for installation, maintenance, maintaining hygiene standards and for use, including storage and handling requirements, as well as, to the extent that such information is available, information to be placed on the label, and instructions for use to be provided with the device when placed on the market. In addition, information relating to any relevant training required.

2.3. Pre-clinical evaluation based on relevant pre-clinical testing and experimental data, in particular regarding in-design calculations, *in vitro* tests, *ex vivo* tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, evaluation of biocompatibility and biological safety, as applicable.

2.4. Existing clinical data, in particular:

— from relevant scientific literature available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of the device and/or of equivalent or similar devices;

— other relevant clinical data available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of equivalent or similar devices of the same manufacturer, including length of time on the market and a review of performance, clinical benefit and safety-related issues and any corrective actions taken.

2.5. Summary of the benefit-risk analysis and the risk management, including information regarding known or foreseeable risks, any undesirable effects, contraindications and warnings.

2.6. In the case of devices that incorporate a medicinal substance, including a human blood or plasma derivative or devices manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives, detailed information on the medicinal substance or on the tissues, cells or their derivatives, and on the compliance with the relevant general safety and performance requirements and the specific risk management in relation to the substance or tissues, cells or their derivatives, as well as evidence for the added value of incorporation of such constituents in relation to the clinical benefit and/or safety of the device.

2.7. A list detailing the fulfilment of the relevant general safety and performance requirements set out in Annex I, including the standards and CS applied, in full or in part, as well as a description of the solutions for fulfilling the relevant general safety and performance requirements, in so far as those standards and CS have not or have only been partly fulfilled or are lacking.

2.8. A detailed description of the clinical procedures and diagnostic tests used in the course of the clinical investigation and in particular information on any deviation from normal clinical practice.

3. Clinical Investigation Plan

The clinical investigation plan (CIP) shall set out the rationale, objectives, design methodology, monitoring, conduct, record-keeping and the method of analysis for the clinical investigation. It shall contain in particular the information as laid down in this Annex. If part of this information is submitted in a separate document, it shall be referenced in the CIP.

3.1. General

3.1.1. Single identification number of the clinical investigation, as referred to in Article 70(1).

3.1.2. Identification of the sponsor — name, address and contact details of the sponsor and, where applicable, the name, address and contact details of the sponsor's contact person or legal representative in accordance with Article 62(2) established in the Union.

3.1.3. Information on the principal investigator at each investigational site, the coordinating investigator for the investigation, the address details for each investigational site and the emergency contact details for the principal investigator at each site. The roles, responsibilities and qualifications of the various kinds of investigators shall be specified in the CIP.

3.1.4. A brief description of how the clinical investigation is financed and a brief description of the agreement between the sponsor and the site.

3.1.5. Overall synopsis of the clinical investigation, in an official Union language determined by the Member State concerned.

3.2. Identification and description of the device, including its intended purpose, its manufacturer, its traceability, the target population, materials coming into contact with the human body, the medical or surgical procedures involved in its use and the necessary training and experience for its use, background literature review, the current state of the art in clinical care in the relevant field of application and the proposed benefits of the new device.

3.3. Risks and clinical benefits of the device to be examined, with justification of the corresponding expected clinical outcomes in the clinical investigation plan.

3.4. Description of the relevance of the clinical investigation in the context of the state of the art of clinical practice.

3.5. Objectives and hypotheses of the clinical investigation.

3.6. Design of the clinical investigation with evidence of its scientific robustness and validity.

3.6.1. General information such as type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan.

3.6.2. Information on the investigational device, on any comparator and on any other device or medication to be used in the clinical investigation.

3.6.3. Information on subjects, selection criteria, size of investigation population, representativeness of investigation population in relation to target population and, if applicable, information on vulnerable subjects involved such as children, pregnant women, immuno-compromised or, elderly subjects.

3.6.4. Details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors.

3.6.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice.

3.6.6. Monitoring plan.

3.7. Statistical considerations, with justification, including a power calculation for the sample size, if applicable.

3.8. Data management.

3.9. Information about any amendments to the CIP.

3.10. Policy regarding follow-up and management of any deviations from the CIP at the investigational site and clear prohibition of use of waivers from the CIP.

3.11. Accountability regarding the device, in particular control of access to the device, follow-up in relation to the device used in the clinical investigation and the return of unused, expired or malfunctioning devices.

3.12. Statement of compliance with the recognised ethical principles for medical research involving humans, and the principles of good clinical practice in the field of clinical investigations of devices, as well as with the applicable regulatory requirements.

3.13. Description of the Informed consent process.

3.14. Safety reporting, including definitions of adverse events and serious adverse events, device deficiencies, procedures and timelines for reporting.

3.15. Criteria and procedures for follow-up of subjects following the end, temporary halt or early termination of an investigation, for follow-up of subjects who have withdrawn their consent and procedures for subjects lost to follow-up. Such procedures shall for implantable devices, cover as a minimum traceability.

3.16. A description of the arrangements for taking care of the subjects after their participation in the clinical investi- gation has ended, where such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

3.17. Policy as regards the establishment of the clinical investigation report and publication of results in accordance with the legal requirements and the ethical principles referred to in Section 1 of Chapter I.

3.18. List of the technical and functional features of the device, with specific mention of those covered by the investi- gation.

3.19. Bibliography.

4. Other information

4.1. A signed statement by the natural or legal person responsible for the manufacture of the investigational device that the device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.

4.2. Where applicable according to national law, copy of the opinion or opinions of the ethics committee or committees concerned. Where according to national law the opinion or opinions of the ethics committee or committees is not required at the time of the submission of the application, a copy of the opinion or opinions shall be submitted as soon as available.

4.3. Proof of insurance cover or indemnification of subjects in case of injury, pursuant to Article 69 and the corresponding national law.

4.4. Documents to be used to obtain informed consent, including the patient information sheet and the informed consent document.

4.5. Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data, in particular:

— organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

— a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects; and

— a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects.

4.6. Full details of the available technical documentation, for example detailed risk analysis/management documentation or specific test reports, shall, upon request, be submitted to the competent authority reviewing an application.

CHAPTER III

OTHER OBLIGATIONS OF THE SPONSOR

1. The sponsor shall undertake to keep available for the competent national authorities any documentation necessary to provide evidence for the documentation referred to in Chapter II of this Annex. If the sponsor is not the natural or legal person responsible for the manufacture of the investigational device, that obligation may be fulfilled by that person on behalf of the sponsor.

2. The Sponsor shall have an agreement in place to ensure that any serious adverse events or any other event as referred to in Article 80(2) are reported by the investigator or investigators to the sponsor in a timely manner.

3. The documentation mentioned in this Annex shall be kept for a period of at least 10 years after the clinical investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. In the case of implantable devices, the period shall be at least 15 years.

   Each Member State shall require that this documentation is kept at the disposal of the competent authorities for the period referred to in the first subparagraph in case the sponsor, or its contact person or legal representative as referred to in Article 62(2) established within its territory, goes bankrupt or ceases its activity prior to the end of this period.

4. The Sponsor shall appoint a monitor that is independent from the investigational site to ensure that the investigation is conducted in accordance with the CIP, the principles of good clinical practice and this Regulation.

5. The Sponsor shall complete the follow-up of investigation subjects.

6. The Sponsor shall provide evidence that the investigation is being conducted in line with good clinical practice, for instance through internal or external inspection.

7. The Sponsor shall prepare a clinical investigation report which includes at least the following:

   — Cover/introductory page or pages indicating the title of the investigation, the investigational device, the single identification number, the CIP number and the details with signatures of the coordinating investigators and the principal investigators from each investigational site.

   — Details of the author and date of the report.

   — A summary of the investigation covering the title, purpose of the investigation, description of the investi- gation, investigational design and methods used, the results of the investigation and conclusion of the investigation. The completion date of the investigation, and in particular details of early termination, temporary halts or suspensions of investigations.

   — Investigational device description, in particular clearly defined intended purpose.

   — A summary of the clinical investigation plan covering objectives, design, ethical aspects, monitoring and quality measures, selection criteria, target patient populations, sample size, treatment schedules, follow-up duration, concomitant treatments, statistical plan, including hypothesis, sample size calculation and analysis methods, as well as a justification.

   — Results of the clinical investigation covering, with rationale and justification, subject demographics, analysis of results related to chosen endpoints, details of subgroup analysis, as well as compliance with the CIP, and covering follow-up of missing data and of patients withdrawing from the clinical investigation, or lost to follow-up.

   — Summary of serious adverse events, adverse device effects, device deficiencies and any relevant corrective actions.
   — Discussion and overall conclusions covering safety and performance results, assessment of risks and clinical benefits, discussion of clinical relevance in accordance with clinical state of the art, any specific precautions specific patient populations, implications for the investigational device,

limitations of the investigation.

A.12 Clinical Trials Transformation Initiative: Assessment of Suitability of Registries Decision Trees and Tables

DECISION TREE 1: EXISTING REGISTRY – HISTORICAL ASSESSMENT

Evaluate if historical evidence generated by an existing registry is robust, relevant, and reliable, with assurance of patient protections

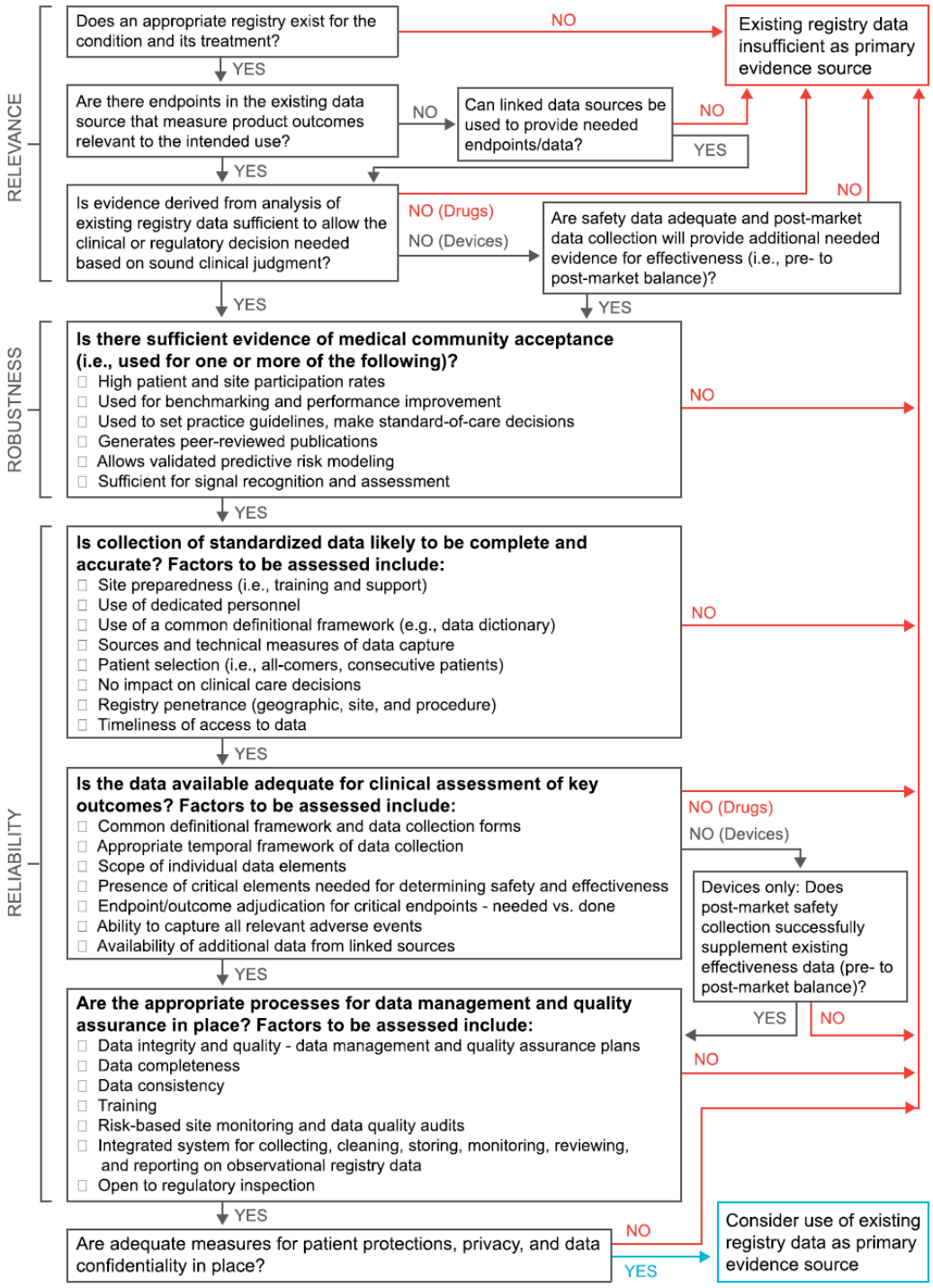

TABLE 1: EXISTING REGISTRY – HISTORICAL ASSESSMENT

Evaluate if historical evidence generated by an existing registry is robust, relevant, and reliable, with assurance of patient protections

Table 1 provides greater detail of the pathway laid out in Decision Tree 1.

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data must demonstrate relevancy and robustness to support regulatory decision-making	**Data are relevant:** 1. Data are adequate in scope and content 2. Data are generalizable: Registry reflects high site and patient participation rates compared with total population **Data are robust—acceptable for use in one or more of the following:** 1. Validated risk prediction 2. Quality assurance 3. Performance improvement 4. Benchmarking 5. Informing practice guidelines 6. Post-market surveillance 7. Generating peer-reviewed publications 8. Comparative effectiveness research	▶ Evaluate if data generated by an existing registry are adequate for evaluating clinical outcomes or supporting regulatory decision-making ▶ Assess whether data and evidence that are generated can address the question at hand (i.e., fit for purpose) ▶ Connectivity: Establish whether there are linkages, or the ability to link to other existing datasets for additional data not captured directly in the registry ▶ Data should be suitable for adequate statistical analysis ▶ Data should be interpretable, i.e., evidence derived from analysis of de-identified aggregate data should be sufficient to allow for regulatory decision-making
Registry data must reliably be able to support regulatory decision-making	**Design:** The registry should be designed to capture reliable data from real-world practice (no protocol-driven treatment)	▶ A standard operating procedure document should exist that defines the processes and procedures for data capture and management ▶ The system should have a basic validation package to assure that the software acts as intended
	Patient population: The patient population should be limited to those with specific diseases, conditions, or treatment exposure(s)	▶ The patient population for the registry is associated with a specific disease, condition, family of procedures (e.g., orthopedic surgery), or treatment exposure(s) ▶ Inclusion and exclusion criteria should be clearly defined (e.g., total population or population subset)

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data must reliably be able to support regulatory decision-making *(continued)*	**Data collection forms:** The data collection forms should be standardized	▶ The existing data elements should be fixed and predefined ▶ There should be an audit trail for any changes ▶ The forms should use standard and uniform data definitions
	Datasets: Data elements should be able to be mapped to industry standards to allow for more direct comparison of data analyses	▶ Documentation should be available that describes the data elements and datasets
	Timing of endpoints/outcomes: The timepoints of each endpoint/outcome in the data collection form should be documented	▶ Evaluate the ability to calculate timing of treatment and treatment outcome (e.g., stroke at discharge or at 30 days post index procedure)
	Timing of data collection: Data collection/entry can occur at any time	▶ The system should be live 24/7 and web-based
	Data completeness and accuracy: Data should be complete, accurate, and attributable	▶ Missing data should be minimized and statistically assessed ▶ Assure processes are in place for data collection and entry with documented training ▶ The system should allow identification of the data originator (e.g., person[s] performing procedure[s]), data source (e.g., point of care, EHR, procedural record), and data entry person ▶ Data logic checks should be included at the time of data entry ▶ Processes should be in place to assure accuracy of the data
Registry has assurance of patient protections	**Documentation of informed consent or IRB waiver of informed consent is needed for access to the data** (e.g., by investigators, patients, regulators) **Patient privacy must be assured:** Assess for use of de-identified data vs. line-item data (informed consent is required for line-item data)	▶ Access to the data needs to be supported by patient informed consent or IRB waiver of informed consent ▶ Use a single IRB of record where possble with a broad-use informed consent document ▶ Data encryption and security protections should be in place ▶ Control/ownership of proprietary data should be addressed

DECISION TREE 2: EXISTING REGISTRY – SUITABILTY ASSESSMENT*

Evaluate elements in an existing registry needed to conduct a clinical trial

*Decision Tree/Table 1 assessment must be made before Decision Tree/Table 2 assessment.

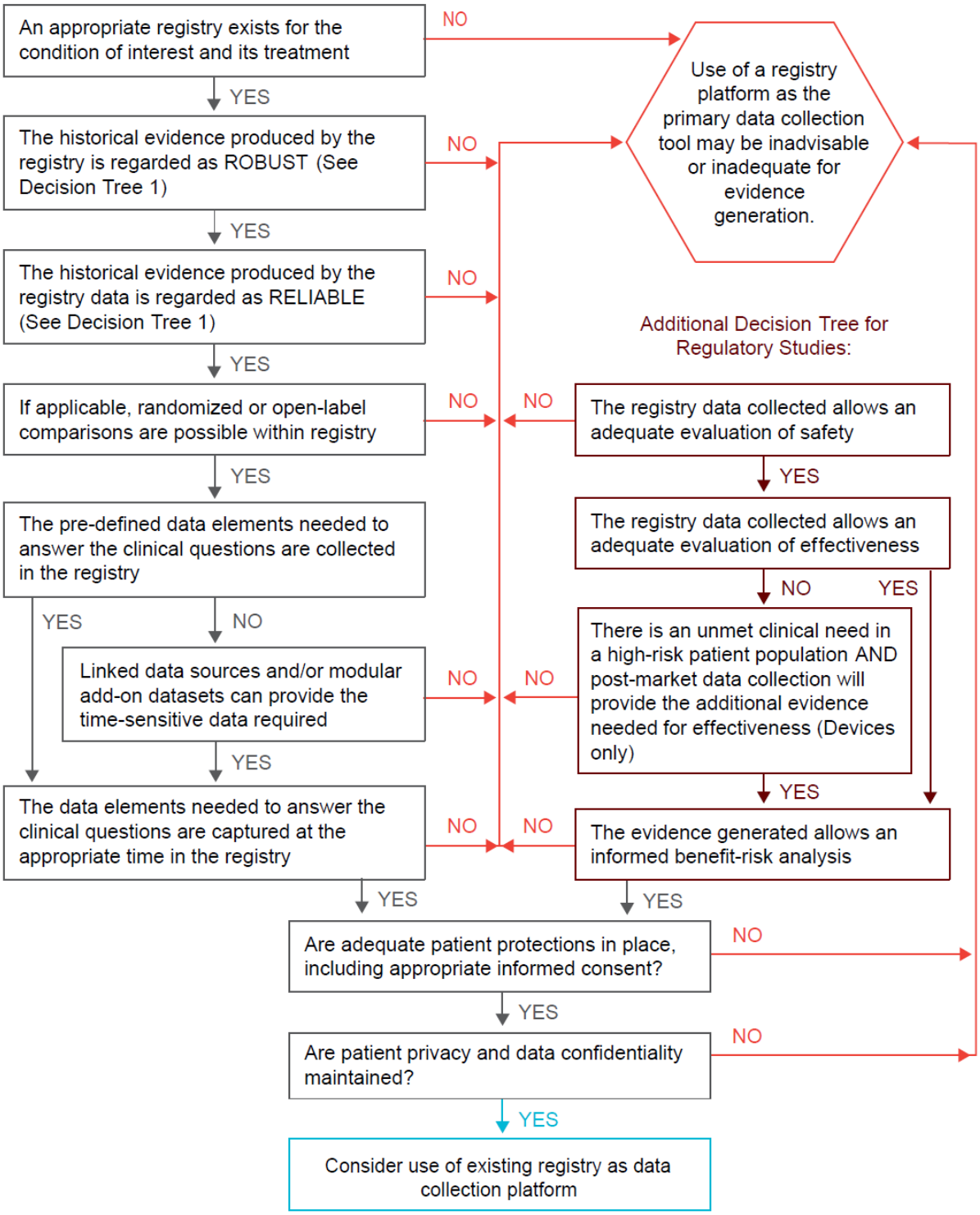

TABLE 2: EXISTING REGISTRY – SUITABILTY ASSESSMENT*

Evaluate elements in an existing registry needed to conduct a clinical trial

Table 2 provides greater detail of the pathway laid out in Decision Tree 2.

*Decision Tree/Table 1 assessment must be made before Decision Tree/Table 2 assessment.

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry must be able to support the proposed clinical trial	1. The existing registry is appropriately focused on the patient population, disease and intervention of interest 2. Historically, the evidence collected within the registry is robust (see Table 1) 3. Historically, the evidence collected within the registry is reliable (see Table 1)	▶ See Table 1 for recommended assessment of a registry for use as the data collection platform for conducting prospective randomized clinical trials, including assessment of applicability, strengths, and weaknesses based on historical use
Registry data must be fit for purpose (relevant)	1. **Assignment of therapy:** Processes must be integrated for identification, assignment, and documentation of eligible participants	▶ Assess ability to incorporate methods required for identification of study-appropriate patients ▶ Evaluate ability to embed processes for randomization into registry workflow ▶ Evaluate ability to embed processes for assurance and documentation of informed consent
	2. **Adequacy of data:** Assure available data elements collected in the registry generate the information/evidence needed to answer the question at hand	▶ Supplement missing and/or longitudinal data elements needed for evidence generation through the use of modular add-on datasets or linkages to other datasets ▶ The eventual goal should be linkage to the EHR for procedural and long-term data collection and incorporation of data collection into the normal workflow
	3. **Ensure availability of appropriate data and analysis tools**	▶ Identify analysis tools necessary to allow the data collected within the registry to generate interpretable results (i.e., evidence) • Develop pre-specified endpoints and a statistical analysis plan • Consider suitability of the totality of the data (i.e., body of evidence supporting the clinical benefit-risk assessment)

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data must be of sufficient quality (reliable) to support a prospective clinical trial	1. **Data collection must be sufficient to support regulatory decision-making** 2. **Data should be complete and accurate**	▶ Assess the adequacy of the registry's data collection form as a case report form (CRF) ▶ Assure appropriately-trained personnel are available at study sites for data collection and abstraction ▶ Registry should incorporate use of a uniform data dictionary ▶ Registry should incorporate appropriate defined timing for collection of key data points
	3. **Employ adequate data quality assurance procedures**	▶ Assess the need for enhanced auditing and monitoring of data to assure completeness and accuracy
	4. **Establish processes for accountability of study subjects**	▶ Minimize patient withdrawals ▶ Minimize patients lost to follow-up
	5. **Source data should be available for key data elements; site-reported data without independent assessment may not provide enough accuracy for key outcomes in randomized trials**	▶ Use independent assessors for key data, such as: • Independent blinded core labs when needed for data interpretation • Clinical Events Committee when needed for adjudication of key outcomes and adverse event data
Registry data and evidence generated must be accessible, with adequate provisions for patient privacy and data confidentiality	1. **Establish data availability to the sponsor and/or clinical investigators, with considerations for patient privacy and data confidentiality**	▶ Assure informed consent adequately describes data accessibility and maintenance of patient privacy and data confidentiality ▶ Assure accurate identification of all study-enrolled patients within registry ▶ Assure ability to sequester records of study-enrolled patients (i.e., patient privacy and data confidentiality) ▶ Define timing and timeliness of sequestered record transfer for sponsor (i.e., product specific proprietary data) ▶ Define timing and timeliness of data transfer to analytic data set
	2. **Ensure availability of line-item data to regulators**	▶ Define timing and timeliness of data and analysis transfer to regulators

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data and evidence generated must be accessible, with adequate provisions for patient privacy and data confidentiality *(continued)*	3. **Establish necessary associations to other data sources**	▶ Determine and provide the necessary linkages to other registries, administrative or government databases, EHRs, etc. ▶ Identify new records generated in linked databases for longitudinal follow-up of patients enrolled in research studies
	4. **Develop plan for data dissemination**	▶ Define timing and timeliness of data transfer to the study sponsor(s) for dissemination of outcome analyses to study participants and participating physicians ▶ As appropriate, define process for release of data and analyses to other stakeholders (e.g., ClinicalTrials.gov, payers, etc.)

TABLE 3: DESIGNING A NEW REGISTRY

Designing a new registry with the capability of embedding a clinical trial suitable for regulatory decision-making

REQUIREMENTS	RECOMMENDATIONS
Clearly articulate the concept of the registry in a transparent manner	The registry design document should articulate the vision, mission, reason, and value proposition of the registry
Define and describe participant characteristics	1. The registry must minimize barriers for inclusion, thus maximizing inclusion of those having the disease/condition to be studied 2. The registry must allow for disparate treatment modalities, including drugs, biologics, devices, and combination products
Select clinically relevant data elements	1. Data elements should efficiently capture and convey information in order to provide evidence based on meaningful clinical endpoints and outcomes 2. Definitions used for data elements should conform to recorgnized standards and nomenclature 3. There must be the ability to: ▶ document informed consent ▶ document randomization/assignment of patients ▶ configure/add additional data elements 4. There should be the ability to: ▶ identify clinically eligible patients for trial participation ▶ accept external data if not collected in the registry (e.g., EHR, reliable external datasets) ▶ measure product performance ▶ document adjudication or core lab determinations for key trial outcomes
Data collection processes must be systematic, consistent, reproducible, and reliable	1. The registry must be 21CFR Part 11 compliant 2. Data traceability must include attributability of data originators and data entry personnel, with date and time stamps for all transactions 3. Data should be usable for clinical care purposes 4. Data collection should be integrated into the process of care 5. All processes must be supported by documented training and education of those entering data (e.g., data managers, data entry personnel, and registry participants)

REQUIREMENTS	RECOMMENDATIONS
Assure the registry conforms to informatics standards	The registry should support: 1. Publication of the data dictionary 2. Defined and semantic interoperational data elements 3. Use of common data elements/controlled vocabularies 4. Use of a common data model 5. Use of the FDA's Unique Device Identifier (UDI), if device 6. Referential integrity via use of single source (e.g., RxNorm, GUDID)
Evaluate and assure data quality across multiple dimensions	The data must be contemporaneous, accurate, legible, consistent, complete, and reliable
Patient protections must be assured	Assure patient protections by including the following elements: 1. Documentation of appropriate informed consent 2. Data confidentiality policies 3. System security compliance and security audits 4. Published explanation of intentional data uses 5. Training of data originators (i.e., data entry personnel) and managers 6. IRB oversight and review
Assure registry design is valid across multiple stakeholder analyses	1. Data should support pre- and post-market regulatory as well as other stakeholder evidentiary needs 2. Data ownership and access to trial-specific data should be established prior to the start of an embedded trial (e.g., processes for sequestration of trial data from the full registry data and access limitations prior to product approval) 3. For site-based users, the registry should support: ▶ Quality assurance and performance improvement ▶ Risk reduction ▶ Benchmarking based on risk-adjusted outcomes 4. Anticipate distributed query and aggregate analysis
Incorporate patient-reported information within the registry	1. Provide guidelines for participants in reporting to the registry 2. Provide technologies/structures to support the systematic, periodic query of participants

A.13 Supplement Table: Definitions and recommendations for primary studies of medical devices from ISO standards

Topic	Definition or Recommendation	Technology	References
RM definition	"Systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk [SOURCE: ISO/IEC Guide 63."	All MD	ISO 14791 3.24
General requirements RM system: RM process	"The manufacturer shall establish, implement, document and maintain an ongoing process for: a) identifying hazards and hazardous situations associated with a medical device; b) estimating and evaluating the associated risks; c) controlling these risks, and d) monitoring the effectiveness of the risk control measures. This process shall apply throughout the life cycle of the medical device. This process shall include the following elements: risk analysis; risk evaluation; risk control; and production and post-production activities."	All MD	ISO 14791 4.1
RM elements Risk analysis	Risk analysis consists of 4 elements: documentation of intended use and reasonably foreseeable misuse of the particular device being considered, identification of characteristics related to safety, identification of hazards and hazardous situations, and risk estimation	All MD	ISO 14791 4.1 Figure 1, 5.2-5.5
RM/ risk analysis	"NOTE 1 If a risk analysis or other relevant information is available for a similar medical device, that analysis or information can be used as a starting point for the new risk analysis. The degree of relevance depends on the differences between the medical devices and whether these introduce new hazards or significant differences in outputs, characteristics, performance or results. The extent of use of an existing risk analysis is based on a systematic evaluation of the effects that the differences can have on the occurrence of hazardous situations."	All MD	ISO 14791 5.1

Topic	Definition or Recommendation	Technology	References
	"NOTE 3 The scope of the *risk analysis* can be very broad (as for the development of a new *medical device* with which a *manufacturer* has little or no experience) or the scope can be limited (as for analysing the impact of a change to an existing *medical device* for which much information already exists in the *manufacturer's* files)."	All MD	ISO 14791 5.1
RM/ risk analysis/ intended use and foreseeable misuse	"The intended use should take into account information such as the intended medical indication, patient population, part of the body or type of tissue interacted with, user profile, use environment, and operating principle. The manufacturer shall also document reasonably foreseeable misuse." "Reasonably foreseeable misuse is defined as use of the medical device in a way not intended by the manufacturer, but which can result from readily predictable human behaviour. This can relate to use error (slip, lapse or mistake), intentional acts of misuse, and intentional use of the medical device for other (medical) applications than intended by the manufacturer"	All MD	ISO 14791 5.2 ISO 24791 5.2
RM/ risk analysis / Safety	"For the particular medical device being considered, the manufacturer shall identify and document those qualitative and quantitative characteristics that could affect the safety of the medical device. Where appropriate, the manufacturer shall define limits of those characteristics." "The questions in Annex A cover many aspects of medical devices and can assist in identifying the characteristics related to safety. For every question, it is indicated which factors should be considered in further detail, with the ultimate goal of identifying all hazards and hazardous situations associated with the medical device"	All MD	ISO 14791 5.3 ISO 24791 5.3 and Annex A

Topic	Definition or Recommendation	Technology	References
	"The list of questions in Annex A should not be used as a check list. It can also be helpful to review available information and literature, including adverse event reports, for similar medical devices." Annex A contains 37 questions on characteristics of the intended use or the MD that may assist in determining whether they could affect safety. "These lists are neither exhaustive nor representative of all medical devices, and the manufacturer is advised to add questions that can have applicability to the particular medical device and to skip questions that are not relevant. The manufacturer is also advised to consider each question not only on its own but also in relation to others. The manufacturer may further consult relevant clinical literature, applicable regulations, or the essential principles of safety and performance for medical devices in ISO 16142-1 …"		
RM/ risk analysis / hazards	"A hazard is a potential source of a harm. Depending on the specific situation, hazards can have different origins/natures." "The manufacturer shall identify and document known and foreseeable hazards associated with the medical device based on the intended use, reasonably foreseeable misuse and the characteristics related to safety in both normal and fault conditions. For each identified hazard, the manufacturer shall consider the reasonably foreseeable sequences or combinations of events that can result in a hazardous situation, and shall identify and document the resulting hazardous situation(s)."	All MD	ISO 24791 5.4 ISO 14791 5.4
RM/ Fundamental risk concepts	"According to the definitions, a hazard cannot result in harm until such time as a sequence of events or other circumstances (including normal use) lead to a hazardous situation. At this point, the risk can be assessed by estimating both severity and probability of occurrence of	All MD	ISO 14791 Annex C

Topic	Definition or Recommendation	Technology	References
	harm that could result. The probability of occurrence of harm can be expressed as a combination of separate probabilities (P1, P2) or as a single probability (P). A decomposition into P1 and P2 is not mandatory.		
RM/ risk analysis / hazards	"A good starting point for this compilation [of hazards] is a review of experience with the same and similar types of medical devices. The review should take into account a manufacturer's own experience and,where appropriate, the experience of other manufacturers as reported in adverse event databases, publications, scientific literature and other available sources. This type of review is particularly useful for the identification and listing of typical hazards and hazardous situations for a medical device and the associated harm that can occur."	All MD	ISO 14791 Annex C
RM/ risk analysis / hazardous situations	"A hazardous situation occurs when people, property or the environment are exposed to one or more hazards. Hazardous situations can arise even when there are no faults, i.e. in the normal condition for the medical device when it is performing as intended. Hazardous situations can be intrinsic aspects of certain therapies." "In cases where a hazardous situation only occurs due to a fault, the probability of a fault occurring is not the same as the probability of the occurrence of harm. A fault can initiate a sequence of events but does not necessarily result in a hazardous situation. A hazardous situation does not always result in harm. It is important to understand that there are generally two types of fault that can lead to a hazardous situation: random and systematic faults."	All MD	ISO 24791 5.4.2 5.4.3
RM Risk estimation	"For each identified hazardous situation, the manufacturer shall estimate the associated risk(s) using available information or data. For hazardous situations for which the probability of the occurrence of harm cannot be estimated, the possible consequences shall be listed for use in risk evaluation and risk control."	All MD	ISO 14791 5.5

Topic	Definition or Recommendation	Technology	References
	NOTE 1 "Risk estimation incorporates an analysis of the probability of occurrence of harm and the severity of the harm." "NOTE 2 Risk estimation can be qualitative or quantitative. Methods of risk estimation, including those resulting from systematic faults, are described in ISO/TR 24971" "NOTE 3 Information or data for estimating risks can be obtained, for example, from:— published standards;— scientific or technical investigations;— field data from similar medical devices already in use, including publicly available reports of incidents;— usability tests employing typical users;— clinical evidence;— results of relevant investigations or simulations;— expert opinion;"		
RM Risk estimation	ISO 14971:2019 requires the manufacturer to perform risk estimation. Various methods can be used to estimate risk. Those methods should examine, for example:— the circumstances in which a hazard is present;— the sequence of events leading to a hazardous situation;— the probability of a hazardous situation occurring; — the probability of a hazardous situation leading to harm;— the nature of the harm that could result. Risk should be expressed in terms that facilitate decision making on risk acceptability and the need for risk control, for example, using severity and probability scales. In order to analyse risks, their components, i.e. probability and severity, should be analysed separately." … "A risk chart such as that shown in Figure 2 [X=probability of occurrence of harm Y= severity of harm] shows the distribution of the estimated risks, which can be useful for later decision making."	All MD	ISO 24791 5.5.1

Topic	Definition or Recommendation	Technology	References
	"If a risk chart or risk matrix is used for ranking risks, the particular risk chart or risk matrix and the interpretation used should be justified for that application.		
Probability of occurrence of harm	"When sufficient data are available to estimate the probability of occurrence of harm with adequate confidence, a quantitative method should be used. Otherwise, a qualitative method based on expert judgment is preferable to a quantitative estimate with high uncertainty. An example of this situation is a new medical device where suitable quantitative data are not available until design validation or later when post-production data become available. For a qualitative method, the manufacturer can describe a series of probability levels with descriptors appropriate for the medical device." "Although probability is a continuous variable, a number of discrete levels can be used in practice to simplify the analysis. The manufacturer decides how many probability levels are appropriate, based on the expected confidence in the estimates. A larger number of probability levels can be used when estimates are made with greater confidence. At least three levels should be identified to facilitate decision making. The levels can be descriptive and qualitative (e.g. not expected to occur during the lifetime of the medical device, likely to occur a few times, likely to occur frequently, etc.) or quantitative. Manufacturers should define the levels explicitly, so that there will be no confusion over what falls within each level. A particularly effective way is to assign ranges of non-overlapping numerical values to the discrete levels." "The definitions of the probability ranges can be the same or different for different product families." There are several factors that are important for estimating the probability of occurrence of harm. These include, but are not limited to, the following.— How often is a particular medical	All MD	ISO 24791 5.5.2 5.5.3

Topic	Definition or Recommendation	Technology	References
	device used?— What is the lifetime of the medical device?— Who makes up the user and patient populations?— What is the number of users/patients? — How long and under what circumstances is the user/patient exposed? "When the probability of occurrence of harm cannot be estimated, it is necessary to evaluate the risk on the basis of the severity of harm alone. The risk control measures should focus on preventing the hazardous situation entirely or on preventing that the hazardous situation leads to harm. If this is not possible, the risk control measures should focus on reducing the severity of the harm.		
Severity of harm	"Severity levels are chosen and justified by the manufacturer based on the harms that could result for a particular medical device. The severity levels should be defined with sufficient specificity, so that the correct level of severity can be assigned to each harm identified in the risk analysis."	All MD	ISO 24791 5.5.4
Risk estimation / Matrix	"Several approaches can be used for qualitative analysis. A typical approach is to use an N-by-M matrix to describe the severities and probabilities of occurrence of harm associated with each hazardous situation. One carefully defines N levels of probability and M levels of severity. Each cell of the matrix represents a subset of the full set of possible risks." "Rationales for the selection of matrices and their outcome scores should be documented."	All MD	ISO 24791 5.5.5
RM elements Risk assessment	Risk assessment definition: overall process comprising a risk analysis and a risk evaluation	All MD	ISO 14791 3.20

Topic	Definition or Recommendation	Technology	References
RM elements Risk evaluation	"For each identified hazardous situation, the manufacturer shall evaluate the estimated risks and determine if the risk is acceptable or not, using the criteria for risk acceptability defined in the risk management plan." "If the risk is acceptable, … the estimated risk shall be treated as residual risk. If the risk is not acceptable, then the manufacturer shall perform risk control activities […]". "ISO 14971:2019 describes the process for risk evaluation. The standard, however, does not specify levels of acceptable risk. The criteria for risk acceptability are based on the manufacturer's policy for determining acceptable risk and are documented in the risk management plan."	All MD	ISO 14791 4.1 Figure 1, 6. ISO 24791 6.
Criteria for risk acceptability	"The criteria for risk acceptability are based on the manufacturer's policy for determining acceptable risk and are documented in the risk management plan." "The policy [for establishing criteria for risk acceptability] provides a framework for establishing the criteria for risk acceptability. This framework directs and guides the establishing of the criteria. This concerns both the criteria for acceptability of individual residual risks and the criteria for acceptability of the overall residual risk." A policy for establishing the criteria for risk acceptability can typically address the following elements:— purpose; — scope;— factors and considerations for determining acceptable risk;— approaches to risk control;— requirements for approval and review." "The purpose describes the goals of the policy for establishing criteria for risk acceptability." "The scope specifies to whom, where and when the policy applies."	All MD	ISO 24791 6. Annex C C.2 C.3

Topic	Definition or Recommendation	Technology	References
	"The following factors and considerations should be taken into account when establishing the criteria for risk acceptability: — Applicable regulatory requirements in the regions where the medical device is to be marketed; —relevant international standards for the particular type of medical device, including standards for testing of specific properties with approval/rejection limits (see also Annex E); — The generally acknowledged state of the art, which can be determined from a review of international standards, best practices in technology, results of accepted scientific research, publications from authorities, and other information for similar medical devices and similar other products. — Validated concerns from stakeholders, for example obtained through direct communication from users, clinicians, patients or regulatory bodies, or through indirect communication via news reports, social media or patient forums. It is important to consider that the perception and understanding of risk acceptability can vary between different groups of stakeholders and can be influenced by their background and the nature of their interest." "Specific criteria can be established for each type of medical device (or medical device family), dependent on its characteristics and intended use, or the same criteria can be applied to all medical devices." "The criteria for risk acceptability can include combinations of qualitative requirements and quantitative limits for specific properties, preferably based on international standards"		
RM elements Risk control	Risk control consists of 6 elements: risk control option analysis, implementation of risk measures, residual risk evaluation, benefit-risk analysis, risks arising from risk control measures, completeness of risk control	All MD	ISO 14791 4.1 Figure 1

Topic	Definition or Recommendation	Technology	References
Risk control	"NOTE 1 The manufacturer's policy for establishing criteria for risk acceptability can define the approaches to risk control: reducing risk as low as reasonably practicable, reducing risk as low as reasonably achievable, or reducing risk as far as possible without adversely affecting the benefit-risk ratio." "Another possible approach to risk control can be related to the magnitude of the risk, for example that risk control can be omitted for small risks below a certain limit."	All MD	ISO 14791 4.2 ISO 24791 Annex C.2
Risk control measures	The manufacturer shall determine risk control measures that are appropriate for reducing the risks to an acceptable level. The manufacturer shall use one or more of the following risk control options in the priority order listed: a) inherently safe design and manufacture; b) protective measures in the medical device itself or in the manufacturing process; c) information for safety and, where appropriate, training to users." "Generally, international standards can be considered to represent the generally acknowledged state of the art. By applying a standard, the manufacturer can simplify the task of analysing residual risks, but it is emphasised that the standard might not address all risks associated with a medical device. Many standards address inherent safety, protective measures, and information for safety for medical devices. When relevant standards exist, they can address some or all risks associated with a particular medical device. The manufacturer can presume that, in the absence of objective evidence to the contrary, meeting the requirements of the relevant standards results in particular risks being reduced to an acceptable level. See Annex E for further guidance on the use of international standards."	All MD	ISO 14791 7.1 ISO 24791 7.1.3

Topic	Definition or Recommendation	Technology	References
Risk control measures	"ISO 14971: 2019 requires implementation of risk control measures, verification of implementation and verification of the effectiveness of those risk control measures. The risk management plan specifies how the two distinct verification activities will be carried out." …" Verification of the effectiveness of the risk control measures in the medical device can require testing of individual risk control measures or testing the medical device. The verification requirements apply to all risk control measures, including information for safety. Testing with users can provide useful information supporting the verification of effectiveness, for example usability testing (see IEC 62366-1, clinical investigation (see ISO 14155)…"	All MD	ISO 24791 7.2
Residual risk evaluation	"After the risk control measures are implemented, the manufacturer shall evaluate the residual risk using the criteria for risk acceptability defined in the risk management plan." "Residual risks are evaluated by the same method and with the same criteria for risk acceptability as the initial risks. The residual risk is either acceptable or unacceptable. When unacceptable, further risk control options should be investigated. If further risk control is not practicable, a benefit-risk analysis may be performed. Residual risk evaluation can be repeated through the life cycle of the medical device, when production and post-production information indicate that either the risk or its acceptability could have changed."	All MD	ISO 14791 7.3 ISO 24791 7.3
Benefit-risk-analysis	"ISO 14971:2019 allows the manufacturer to perform a benefit-risk analysis for those risks that are not judged acceptable using the criteria established in the risk management plan and for which further risk control is not practicable. The benefit-risk analysis is used to determine if the residual risk is outweighed by the expected benefits of the intended use of the medical device."	All MD	ISO 24791 7.4.1

Topic	Definition or Recommendation	Technology	References
	"Benefit-risk analyses cannot be used to weigh residual risks against business advantages or economic advantages" "The practicability of further risk reduction should be taken into account before considering the benefits (see Annex C). The decision as to whether risks are outweighed by benefits is essentially a matter of judgment by experienced and knowledgeable individuals, usually a multidisciplinary team comprising medical, clinical or application experts. An important consideration is whether an anticipated benefit can be achieved through the use of alternative solutions without that risk or with smaller risk. This involves comparing the residual risk for the manufacturer's medical device with the residual risk for similar medical devices."		
Benefit estimation	"The benefit arising from a medical device is related to the likelihood and extent of improvement of health expected from its use. Benefits can be described in terms of positive impact on clinical outcome, the patient's quality of life, outcomes related to diagnosis, positive impact from diagnostic devices on clinical outcomes, or a positive impact on public health. The nature and degree of benefits can depend on the patient population." "Benefit can be estimated from knowledge of several factors such as:— the performance expected during clinical use;— the clinical outcome expected from that performance;— benefits resulting from the use of similar medical devices;— factors relevant to the risks and benefits of other diagnosis or treatment options. Confidence in the benefit estimate is strongly dependent on the reliability of the information addressing these factors. This includes recognition that there is likely to be a range of possible outcomes." "Due to the difficulties in applying a rigorous approach, it is generally necessary to make simplifying assumptions. Therefore, it will usually prove expedient to focus on the most likely	All MD	ISO 24791 7.4.2

Topic	Definition or Recommendation	Technology	References
	outcomes for each option and those that are the most favourable or unfavourable. The following aspects should be taken into account: — the type of expected benefits for the patient or other people […];— the magnitude of the expected benefits […]; — the probability that the patient will experience the expected benefits[…]); and— the duration of the expected effects[…].” If reliable clinical data demonstrating the consistent performance and effectiveness of the medical device are available, the benefit can be estimated confidently. In cases where clinical data are limited in quantity or quality, benefit is estimated with greater uncertainty from whatever relevant information is available. […]Where significant risks are present and the benefit estimate has a high degree of uncertainty, it will be necessary to verify the anticipated performance or effectiveness through a simulation study or a clinical investigation. This is essential to confirm that the benefit-risk balance is as expected and to prevent unwarranted exposure of patients to a large residual risk. ISO 14155[26] specifies procedures for clinical investigations of medical devices.		
Benefit-risk analysis criteria	“Those involved in making benefit-risk judgments have a responsibility to understand and take into account the technical, regulatory, economic and sociological context of their risk management decisions. This can involve an interpretation of fundamental requirements set out in applicable regulations or standards, as they apply to the medical device under consideration under the anticipated conditions of use. Since this type of analysis is highly product-specific, further guidance of a general nature is not possible. Instead, the safety requirements specified by standards addressing specific products or risks can be presumed to be consistent with an acceptable level of risk, especially where the use of those standards is	All MD	ISO 24791 7.4.3 7.4.4

Topic	Definition or Recommendation	Technology	References
	sanctioned by the prevailing regulatory system. Note that a clinical investigation might be required to verify that the balance between benefit and residual risk is acceptable." "A direct comparison of benefit and risk is complicated and should take the following into account: — characterization of the disease or condition of the intended patients;— the uncertainty of data. Initially, a literature search for the hazards and the medical device being considered can provide insight into the balance between benefit and risk;— production and post-production information for similar medical devices that are already available on the market;— the generally acknowledged state of the art;— a comparison of the benefits of the medical device under development with the benefits of similar medical devices available on the market;— a comparison of the residual risks of the medical device under development with the residual risks of similar medical devices available on the market. ISO 14971:2019 requires the manufacturer to record the results of a benefit-risk analysis in the risk management file. It is recommended to include the rationale how the conclusion was reached."		
RM elements Overall residual risk evaluation	"After all risk control measures have been implemented and verified, the manufacturer shall evaluate the overall residual risk posed by the medical device, taking into account the contributions of all residual risks, in relation to the benefits of the intended use, using the method and the criteria for acceptability of the overall residual risk defined in the risk management plan …" "ISO 14971:2019 requires that the criteria for the acceptability of the overall residual risk be established as well. These can be the same or different from the criteria for acceptability of individual risks."	All MD	ISO 14791 4.1 Figure 1 8. ISO 24791 Annex C.3 ISO 24971 8.1

Topic	Definition or Recommendation	Technology	References
	"The evaluation of overall residual risk is the point where residual risk is viewed from a broad perspective. All identified hazardous situations have been evaluated and all risks have been reduced to an acceptable level or have been accepted based upon a benefit-risk analysis. Now, the manufacturer considers if the overall residual risk associated with the medical device as a whole satisfies the criteria for acceptability of overall residual risk. This consideration takes into account the contributions of all residual risks together in relation to the benefits of the intended use of the medical device. This step is particularly important for complex medical devices and for medical devices with a large number of individual risks" "This consideration takes into account the contributions of all residual risks together in relation to the benefits of the intended use of the medical device. This step is particularly important for complex medical devices and for medical devices with a large number of individual risks." "Ultimately, the evaluation should be based on expert judgment with essential roles for application knowledge and clinical expertise. The results of the evaluation of overall residual risk form part of the risk management file. It is recommended to document the rationale for the acceptance of the overall residual risk." "The results of the design validation, usability studies, clinical evaluations and clinical investigations can provide useful information about the overall residual risk. Appropriate input from stakeholders can provide useful information." "The method to evaluate the overall residual risk can include the following approaches or other approaches deemed appropriate by the manufacturer. a) The benefits related to the intended use of the medical device are weighed against the overall residual risk. Benefits can be described by their magnitude or extent, the probability of experiencing the benefit within		8.2 8.3

Topic	Definition or Recommendation	Technology	References
	the intended patient population, and the duration and frequency of the benefit. The evaluation should take into account knowledge of the intended medical indication, the generally acknowledged state of the art in technology and medicine, and the availability of alternative medical devices or treatments. […] c) The manufacturer can compare the medical device under consideration to similar medical devices available on the market. The key question is whether the medical device under consideration has an acceptable overall residual risk in relation to the medical benefits, in comparison to similar medical devices. Residual risks posed by the medical device can be compared individually to corresponding risks for the similar medical device, taking account of differences in intended use. Up-to-date information on intended use and adverse events of similar medical devices should be carefully reviewed, as well as information from scientific literature, including information about clinical experience. d) The manufacturer can use experts to support the evaluation of the overall residual risk in relation to the benefits expected from using the medical device under consideration. These experts can come from a variety of disciplines and should include those with clinical or application experience and those with knowledge of similar medical devices. The experts should have an appropriate level of independence from those who designed and developed the medical device. They can assist the manufacturer in taking into account stakeholder concerns. Attention is drawn to the requirements in ISO 14971:2019 for training and experience. e) Even though all individual risks should have been identified, controlled and judged acceptable at this point, it could be appropriate that some risks are investigated further as a result of the overall residual risk evaluation. For example, there could be many risks close to		

Topic	Definition or Recommendation	Technology	References
	being not acceptable. Hence, the overall residual risk could not be deemed acceptable, and a further investigation would be appropriate. f) Further investigation can also be appropriate when some risks are interdependent with respect to either their causes or the risk control measures applied. Risk control measures should be verified for effectiveness, not only individually but also in combination with other risk control measures. This can also apply to risk control measures designed to control multiple risks simultaneously. Fault Tree Analysis (FTA) or Event Tree Analysis (ETA) can be useful tools to discover such relationships between risks and risk control measures."		
RM elements risk management review	"Prior to release for commercial distribution of the medical device, the manufacturer shall review the execution of the risk management plan. This review shall at least ensure that: — the risk management plan has been appropriately implemented; — the overall residual risk is acceptable; and — appropriate methods are in place to collect and review information in the production and post-production phases." "There can be a need to revise or update the risk management report if new information becomes available, for example during the production and post-production phases. The manufacturer determines when subsequent reviews of the execution of the risk management plan and updates of the risk management report are performed, for example, after a major change in the design of the medical device."	All MD	ISO 14791 4.1 Figure 1 9. ISO 24971

Topic	Definition or Recommendation	Technology	References
RM elements production and post-production activities	Production and post-production activities consist of 4 elements: general, information collection, information review, actions "The manufacturer shall establish, document and maintain a system to actively collect and review information relevant to the medical device in the production and post-production phases. When establishing this system, the manufacturer shall consider appropriate methods for the collection and processing of information." "Monitoring of production and post-production information is the critical step that enables medical device manufacturers to close the feedback loop and to make risk management a continuous life cycle process." "Production and post-production activities can include receiving information about the medical device safety and performance. Sources typically include general feedback from users, distributors, service personnel and training personnel. The information can be related to harm that has occurred or to hazardous situations that occurred without harm. The activities can also include soliciting information about the medical device performance and related risks. These activities involve reaching out to stakeholders to obtain specific information and insight, using methods such as customer surveys, expert user groups (focus groups) and manufacturer-sponsored medical device tracking/implant registries. It also includes publicly available information such as clinical literature, incident reports and adverse event databases." "The activities can further include post-market clinical follow-up (PMCF) studies carried out following market approval, which are intended to enhance the clinical evidence for the safety and performance of a medical device after it is placed on the market."	All MD	ISO 14791 4.1 Figure 1 10.1 ISO 24791 10.1 10.2 Table 7 ISO 14971 10.4

Topic	Definition or Recommendation	Technology	References
	"The information collected does not necessarily have to be directly related to the manufacturer's medical device. Other medical devices with similar intended use, similar principle of operation or similar hazards can yield useful information about the risks associated with the manufacturer's medical device." Table 7 lists 9 categories of data sources related to production and post-production: production, complaint handling, service reports, risk management, clinical activities, market/ patient surveys, scientific literature, media sources, security data sources. "The information review can lead to several possible outcomes, for example:— The hazard and hazardous situation were correctly identified. The risk was adequately assessed and remains acceptable.— The hazard and hazardous situation were correctly identified, but the risk has increased and is no longer acceptable. Further action is required.— The hazard or hazardous situation was not identified. Further action is required.— The generally acknowledged state of the art or the benefits for the medical device have changed. Further action is required. Concerning changes in the generally acknowledged state of the art, consideration should also be given to the availability of alternatives to treat or diagnose the medical condition of the intended patients, including the safety and effectiveness and the associated risks of those alternatives. The risks and benefits to patients in situations where no treatment or diagnosis is available should also be considered. The manufacturer should also assess whether the anticipated benefits of the intended use are achieved or have changed. If the benefits change while the risks remain the same, the balance between benefit and overall residual risk can also change."		

Topic	Definition or Recommendation	Technology	References
	"If the collected information is determined to be relevant to safety, the following actions apply.1) Concerning the particular medical device,— the manufacturer shall review the risk management file and determine if reassessment of risks and/or assessment of new risks is necessary;— if a residual risk is no longer acceptable, the impact on previously implemented risk control measures shall be evaluated and should be considered as an input for modification of the medical device;— the manufacturer should consider the need for actions regarding medical devices on the market; and— any decisions and actions shall be recorded in the risk management file. 2) Concerning the risk management process,— the manufacturer shall evaluate the impact on previously implemented risk management activities; and — the results of this evaluation shall be considered as an input for the review of the suitability of the risk management process by top management."		
RM	"Risk management activities shall be performed throughout the clinical investigation."	All MD (except IVD)	ISO 14155 6.2.1
RM	"Risk management principles shall be applied to both the planning and the conduct of clinical investigations, in order to ensure the reliability of the clinical data generated and the safety of subjects."	All MD (except IVD)	ISO 14155 6.2.3
RM	"The sponsor shall identify, assess and control risks associated with clinical investigation processes to ensure the ethical and scientific conduct of the clinical investigation and the credibility of the clinical investigation results."	All MD (except IVD)	ISO 14155 6.2.3
RM / benefit-risk balance	"The decision to embark upon or continue a clinical investigation of an investigational medical device requires that the residual risk(s), as identified in the risk analysis, as well as risk(s) to	All MD (except IVD)	ISO 14155

Topic	Definition or Recommendation	Technology	References
	the subject associated with the clinical procedure including follow-up procedures required by the CIP be balanced against the anticipated benefits to the subjects."		6.2.1
RM / risk assessment MD	"Risks associated with the investigational device and its related clinical procedure shall be estimated in accordance with ISO 14971 prior to design and conduct of a clinical investigation." "The risk assessment shall include or refer to an objective review of published and available unpublished medical and scientific data."	All MD (except IVD)	ISO 14155 6.2.2
RM / risk assessment of clinical procedures /	"Clinical risks related to the clinical procedures, including follow-up procedures required by the CIP other than those related to the medical device, shall be identified from the literature review.	All MD (except IVD)	ISO 14155 6.2.3
RM/ risks/ disclosure	Their [clinical risks related to the clinical procedure] disclosure in the CIP and if applicable, the informed consent, shall also be determined by the sponsor and managed in the interest of subject safety."	All MD (except IVD)	ISO 14155 6.2.3
RM /risk control levels	"Risk control measures should be considered at both the clinical quality management system level (e. g. standard operating procedures, computerized systems, personnel) and clinical investigation planning and conduct (e. g. clinical investigation design, data collection, informed consent process)."	All MD (except IVD)	ISO 14155 6.2.3
RM /risk control/ training	"Where the risk management report's conclusions require training on the investigational device, consideration should be made by the sponsor about the extent of the training (e.g. animal model, cadaver training, support to users throughout the clinical investigation)."	All MD (except IVD)	ISO 14155 6.2.2

Topic	Definition or Recommendation	Technology	References
RM / predefinition of risk thresholds	"For both the investigational device including clinical procedure […] and clinical investigation process […], the sponsor shall predefine or establish risk acceptability thresholds and trigger a risk assessment to determine whether actions are needed as soon as thresholds are reached or exceeded."	All MD (except IVD)	ISO 14155 6.2.1
RM / benefit-risk analysis reporting	A summary of the benefit-risk analysis shall be disclosed in the relevant clinical investigation documents. The residual risk, including the characterization of their nature (hazards), incidence (occurrence), severity and outcome (harms) shall be disclosed in the IB […] and the instructions for use. The level of detail necessary shall be determined by the sponsor and managed in the interest of subject safety." "The CIP shall include all anticipated adverse device effects and a rationale for the related benefit-risk ratio." "All anticipated adverse device effects shall be disclosed in the informed consent form."	All MD (except IVD)	ISO 14155 6.2.2
RM / justification of study	The purpose of the IB is to provide the principal investigator and the investigation site team with sufficient safety or performance data from pre-clinical investigations or clinical investigations to justify human exposure to the investigational device specified in the CIP. The IB shall be updated throughout the course of the clinical investigation as significant new information becomes available (e.g. a significant change in risk)."	All MD (except IVD)	ISO 14155 6.5
Need for CI			
RM / benefit-risk balance	"The decision to embark upon or continue a clinical investigation of an investigational medical device requires that the residual risk(s), as identified in the risk analysis, as well as risk(s) to the subject associated with the clinical procedure including follow-up procedures required by the CIP be balanced against the anticipated benefits to the subjects."	All MD (except IVD)	ISO 14155 6.2.1

Topic	Definition or Recommendation	Technology	References
	See RM		
	"Clinical investigations shall be performed for new heart valve systems and expanded indications for use." For modifications of an existing heart valve system, if a determination is made based on the risk analysis that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided. For design changes of a marketed device that might affect safety and effectiveness (e.g. novel blood-contacting materials, changes that alter the flow characteristics or haemodynamics, and changes that affect the mechanical loading on the valve), the need for a clinical investigation shall be determined and justified on the basis of a risk analysis."		5840-1 7.4
	"Clinical investigations shall be performed for new surgical heart valve systems and expanded indications for use. For modifications of an existing heart valve system, if a determination is made based on the risk analysis that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided. Clinical studies are recommended for design changes of a marketed device that may affect the safety and effectiveness (e.g. novel blood-contacting materials, changes that alter the flow characteristics or haemodynamics, changes that affect the mechanical loading on the valve)."		5840-2 7.4.1
	"Clinical investigations shall be performed for new transcatheter heart valve systems and expanded indications for use of existing systems (e.g. lower risk populations, ViV, ViR).		5840-3 7.4.1

Topic	Definition or Recommendation	Technology	References
	For modifications of an existing transcatheter heart valve system, if a determination is made, based on the risk analysis, that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided. For minor design modifications to clinically well-documented heart valve substitutes, the manufacturer shall justify omission or abbreviation of clinical investigations. Clinical studies are recommended for design changes of a marketed device that may affect the safety and effectiveness (e.g. novel blood-contacting materials, changes that alter the flow characteristics or haemodynamics, changes that affect the mechanical loading on the valve)."		
	"Clinical investigations shall be performed for new or modified heart valve repair devices and expanded indications for use to investigate those risks and aspects of clinical performance that cannot be fully evaluated from pre-clinical or other available data. If a determination is made that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided."		5910 7.4.1
	"An investigation shall be carried out for each new prosthesis or new clinical application of a prosthesis prior to market approval, using the principles given in ISO 14155 or an equivalent publication." "Significant design changes that can impact safety and performance shall require clinical investigation if determined to be necessary based on an appropriate risk assessment."		7198 10.1.1
	"Included in the clinical investigation shall be appropriate testing of any VDDCP incorporating design characteristics for which the safety and effectiveness have not been previously demonstrated."		12471-1 7.3.1

Topic	Definition or Recommendation	Technology	References
	"An investigation shall be carried out for each new implant device or new clinical application of a device prior to market approval, using the principles given in ISO 14155 or an equivalent publication."		17137 5.7.1
	"An investigation should be carried out for each new prosthesis or new clinical application of a prosthesis using the principles given in ISO 14155, or an equivalent publication." "Significant design changes that can impact safety and performance shall require clinical evaluation if determined to be necessary based on an appropriate risk assessment." "Additional prosthesis sizes outside the previously evaluated range might require clinical evaluation."* "Additional stent sizes outside the previously evaluated range might require clinical evaluation but may not require assessment consistent with all requirements (e.g. multicentre study, statistically powered sample size)."** *ISO 25539-1 ** ISO 25539-2		ISO 25539-1 8.7.1 ISO 25539-2 8.7.1
Other means than CI	"If an objective of a clinical study can be met through alternative means (e.g. through reference to previously conducted clinical studies), the use of previously obtained data or other supportive information shall be justified. The justification should include comment on the relevance of any differences between the subject device and the device used in the previous study and the relevance of any differences in the intended uses."		7198 10.1.1 ISO 25539-1 8.7.1 ISO 25539-2 8.7.1

Topic	Definition or Recommendation	Technology	References
Choice of study design			
Study types and development stages	"This annex provides a general indication of the possible types of clinical investigations in different clinical development stages described hereunder and a schematic is given in the Table I.1."	All MD (except IVD)	ISO 14155 Annex I
Development stages definitions	Based on the risk assessment, medical devices can undergo three general stages of clinical development. These stages can be dependent on each other and doing a thorough evaluation in one stage can make the next stage much more straightforward. The clinical investigation population can be influenced by the type of clinical development stage, for example pilot stage population may come from a sub group of the total target population for which the device is eventually indicated." "Pilot stage. 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." Table 7 shows that studies in the pilot stage may be exploratory or confirmatory. "Pivotal stage. 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." Table 7 shows that pivotal studies can only be confirmatory.	All MD (except IVD)	ISO 14155 Annex I I.3.2 I.3.3 I.3.4

Topic	Definition or Recommendation	Technology	References
	"Post-market stage. The post-marketing stage can include additional confirmatory clinical investigations to establish clinical performance or effectiveness of the medical device in a broader population of users and subjects. Observational clinical investigations for better understanding of device safety, such as rare adverse events and long-term outcome, are also included in the post-marketing stage."		
Study types/ regulatory status, definition	"Pre-market clinical investigation. A clinical investigation carried out before market approval of the investigational device. NOTE 1 For the purpose of a pre-market clinical investigation, "market approval" is synonymous with "availability of the medical device in the market". NOTE 2 If marketed products are being investigated for new indications, other than described in the approved labelling, normative directions for pre-market clinical investigations apply. Post-market clinical investigation. A clinical investigation carried out following market approval of a medical device, intended to answer specific questions relating to clinical performance, effectiveness or safety of a medical device when used in accordance with its approved labelling. NOTE 1 For the purpose of post-market clinical investigation "market approval" is synonymous with "availability of the medical device in the market". NOTE 2 Post-market clinical investigation can be part of a post-market clinical follow-up process. If marketed medical devices are being investigated for new indications, other than described in the approved labelling, requirements for pre-market clinical investigations apply. NOTE 3 National regulations can apply.	All MD (except IVD)	ISO 14155 Annex I.2
Study types	"Three main clinical investigation designs can be considered as referenced in I.3 and are further defined hereunder. "I.4.2 Exploratory clinical investigation. A clinical investigation, such as a first in human or feasibility clinical investigation as defined in this annex that might	All MD (except IVD)	ISO 14155 Annex I

Topic	Definition or Recommendation	Technology	References
	not have pre-specified primary hypotheses, and can be conducted to generate hypotheses, to be confirmed in subsequent clinical investigations. I.4.3 Confirmatory clinical investigation. A confirmatory clinical investigation is an adequately controlled clinical investigation in which the hypotheses of the primary endpoint(s) are stated before the start of the clinical investigation in the CIP and are analysed in accordance with the CIP (i.e. sound confirmative statistical testing is pre-specified, intended, and applied). I.4.4 Observational clinical investigation. Clinical investigation that draws inferences about the possible effect of an intervention on subjects, but the investigator has not assigned subjects into intervention groups and has not made any attempts to collect data on variables beyond those available throughout the course of normal clinical practice and burden to the subject." "Throughout the above described clinical development stages, different descriptors of clinical investigations can apply, and the most common examples are defined hereunder. I.5.2 First in human clinical investigation. A clinical investigation in which a medical device for a specific indication is evaluated for the first time in human subjects. I. 5. 3 Early feasibility clinical investigation. A limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application). It can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or effectiveness (if appropriate) as per intended use in a small number of subjects when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility clinical investigation can guide device modifications. An early feasibility clinical investigation does not necessarily involve the first		I.4.2 I.4.3 I.4.4 I.5.2 I.5.3 I.5.4 I.5.5 I.5.6 I.6.2 I.6.3

Topic	Definition or Recommendation	Technology	References
	clinical use of a device. NOTE Early feasibility clinical investigation can also be called proof of concept clinical investigation. I. 5.4 Traditional feasibility clinical investigation. A clinical investigation that is commonly used to capture preliminary clinical performance, effectiveness or safety information of a near-final or final device design to adequately plan an appropriate pivotal clinical investigation. Because the clinical investigation of a near-final or final device design takes place later in development than an early feasibility clinical investigation, more non-clinical or prior clinical data are expected than in an early feasibility clinical investigation. A traditional feasibility clinical investigation does not necessarily need to be preceded by an early feasibility clinical investigation. I.5.5 Pivotal clinical investigation. A confirmatory clinical investigation designed to collect data on the clinical performance, effectiveness or safety of a device for a specified intended use, typically in a statistically justified number of human subjects. It can or cannot be preceded by an early and/or a traditional feasibility clinical investigation. I.5.6 Registry. An organized system that uses observational methods to collect defined clinical data under normal conditions of use relating to one or more medical devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose(s). NOTE 1 The term “registry study” is synonymous with “device registry” or “registry”. NOTE 2 Individual registry studies can be used within the context of the IMDRF N33R1 ‘Patient registry; Essential Principles’ registry system (covering multiple applicable registries), […].”		

Topic	Definition or Recommendation	Technology	References
	"Clinical investigations can further be categorized by their nature of interference with normal clinical practice as further defined hereunder. These categorisations are usually referred to for defining the requirements of ethical considerations". I.6.2 Interventional clinical investigation. Interventional clinical investigation is a pre-or post-market clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a CIP or diagnostic or monitoring procedures requested in the CIP are in addition to those available as normal clinical practice and burden the subject. I.6.3 Non-interventional clinical investigation. Non-interventional clinical investigation is a post-market clinical investigation where the medical device is used in accordance with its approved labelling. The assignment of a subject to a particular medical device is not decided in advance by a CIP but falls within current clinical practice. The use of the medical device is clearly separated from the decision to include the subject in the clinical investigation. No additional invasive or burdensome diagnostic or monitoring procedures are applied to the subjects and epidemiological methods are used for the analysis of collected data. NOTE In general, "observational" clinical investigations are "non-interventional".		
Requirements for pre-market CI	"Depending on the clinical development stage and the type of the clinical investigation design, the principles* of this document can be applied in full or in part. Significant exceptions from the requirements of this document should be duly justified and noted in the CIP or other sponsor regulatory files." "a) Pre-market exploratory clinical investigation: all principles in this document apply with the exception that no mandatory (pre-)specification of a statistical hypothesis is required. b) Pre-market confirmatory clinical investigations: all principles in this document apply."		ISO 14155 Annex I.7

Topic	Definition or Recommendation	Technology	References
	* All elements of the normative Annexes A (CIP), B (IB), D (CIR) are required		
Classification of study design	"The study design shall be designated by the following terms: — randomized, multi-arm, "unblinded" study with a concurrent control using an alternative or no treatment; — non-randomized study with concurrent control; — single-arm study with patient serving as own control (include designed single-arm crossover); — single-arm study with historical control using patient-level data; — single-arm study with literature control; — single-arm study with performance goals."	Cardiovascular implants: Tubular vascular grafts and vascular patches Cardiovascular implants: Endovascular prostheses	ISO 7198 10.1.3 ISO 25539-1 8.7.3
	"The study design shall be designated by appropriate terms [e.g. number of study arms, type of control (randomized, literature, performance goal), blinding, prospective vs retrospective]."	Cardiovascular implants: Vascular stents	ISO 25539-2 8.7.3
Choice of study design			
Appropriate study design / preparation	"The justification for the design of the clinical investigation shall be based on the evaluation of pre-clinical data and the results of a clinical evaluation (see References […]) and shall be aligned with the results of the risk assessment."	All MD (except IVD)	ISO 14155 6.3

Topic	Definition or Recommendation	Technology	References
and justification	"The clinical evaluation includes an assessment and analysis of clinical data concerning clinical performance, effectiveness or safety of the investigational device or similar devices or therapies. The evaluation shall be relevant to the intended purpose and the proposed method of use of the investigational device or similar devices or therapies. This is a scientific activity that shall be done with rigour and objectivity according to scientific standards (see References […])." See also risk management / justification		
Appropriate study design / factors to consider	"Several factors are important when designing any medical device clinical investigation, including general considerations of sources of bias and bias minimization, as well as specific considerations related to clinical investigation objectives, subject selection, subject endpoint(s), stratification, investigation site selection, and comparative clinical investigation designs (see A.6 and A.7)"	All MD (except IVD)	ISO 14155 6.3
Appropriate study design / justification for specific factors of design	"The results of the clinical evaluation and the risk assessment shall be used to determine the required clinical development stages (see Annex I) and justify the optimal design of the clinical investigation. They shall also help identify relevant endpoints and confounding factors to be taken into consideration and serve to justify the choice of control group(s) and if applicable, comparator(s), the use of randomization or blinding, and other methods to minimize bias."	All MD (except IVD)	ISO 14155 6.3
Appropriate study design/ objectives	"The clinical investigation shall be designed to evaluate whether the investigational device is suitable for the purpose(s) and the population(s) for which it is intended. It shall be designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives, in particular the benefit-risk profile of the investigational device."	All MD (except IVD)	ISO 14155 6.3

Topic	Definition or Recommendation	Technology	References
	"The clinical investigation should be designed to allow confirmation of the benefit-risk analysis of the investigational device as outlined in the risk management report."		
Appropriate design / Content of CIP justification	**"The CIP shall include the information specified in Annex A. The CIP shall clearly outline the objectives of the clinical investigation. The proposed design shall be adequately justified based on scientific and ethical principles. The objective(s) of the investigation determine(s) whether an exploratory or a confirmatory design is appropriate to ascertain that the objectives of the clinical investigation can be reached."** "A.3 Justification for the design of the clinical investigation. **Justification for the design of the clinical investigation, which shall be based on the conclusions of the clinical evaluation, as specified in 6.3, and shall comprise** **a) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable carried out to justify the use of the investigational device in human subjects,** b) an evaluation of clinical data that are relevant to the proposed clinical investigation, c) a description of the clinical development stage (see Annex I), if appropriate."	All MD (except IVD)	ISO 14155 6.4 Annex A.3
Appropriate study design /life cycle	"The objective(s) of the investigation determine(s) whether an exploratory or a confirmatory design is appropriate to ascertain that the objectives of the clinical investigation can be reached."	All MD (except IVD)	ISO 14155 6.4
	"A prospective randomised controlled trial, assessing superiority or non-inferiority as appropriate, may be considered to minimise bias. Depending on the scope and objectives of the clinical investigation, other designs may be appropriate."		ISO 5840-2 7.4.6.3 ISO 5840-3 7.4.6
	"A randomized controlled trial, assessing superiority or non-inferiority as appropriate, should be considered to minimize bias when existing objective performance and safety metrics are		ISO 5910 7.4.6

Topic	Definition or Recommendation	Technology	References
	inadequate. Depending on the scope and objectives of the clinical investigation, other designs may be appropriate."		
/Pilot study	"Prior to embarking on a pivotal clinical investigation, pilot phase studies shall be considered to provide initial information regarding clinical safety and effectiveness. A scientific justification shall be provided if pilot phase studies are not to be undertaken. The information derived from the pilot phase may be used to optimize device design prior to initiation of a larger clinical investigation following further pre-clinical testing."		ISO 5910 7.4.1 ISO 5840-2 7.4.1 ISO 5840-3 7.4.1
	"A multicentre study shall be performed at a minimum of three investigational sites. A justification for the number of investigational sites shall be provided…. A control should be included in the study to appropriately address the questions postulated. If an appropriate control is not or cannot be identified, or a concurrent control is unnecessary, a method for evaluating the clinical outcomes shall be prospectively defined and justified (e.g. performance goals)." In 25539-1,-2, 12417-1 only: "An appropriate epidemiological approach shall be utilized for recruiting subjects to minimize bias (e.g. encourage sequential enrolment)."		7198 10.1.3 12417-1 7.3.3 25539-1 25539-2 8.7.3
	Refers generally to ISO 14155 and ISO 12417-1		ISO 17137 5.7.3
General design issues			

Topic	Definition or Recommendation	Technology	References
Objective of CI			
Definition	**"Objective: main purpose for conducting the clinical investigation"**	All MD (except IVD)	ISO 14155 3.37
Objective	"The objective(s) shall serve the purpose of the clinical investigation and shall relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population. The objectives of the clinical investigation shall translate directly into the pre-specification and operationalisation of the primary endpoint(s). Claims shall be linked to eligibility criteria for subject and users."		ISO 14155 Annex A.5
	"The purpose of clinical investigation is to assess the safety and effectiveness of a vascular prosthesis. This investigation is not intended to demonstrate the long-term performance of the prosthesis"		ISO 7198 10.1.1
	"The purpose of the clinical evaluation is to provide reasonable assurance of the safety and to evaluate the performance of the VDDCP."		ISO 12417 7.3.1
	"The purpose of clinical evaluation is to evaluate the performance of the delivery system, if applicable, and assess the safety and effectiveness of the absorbable cardiovascular implant."		ISO 17137 5.7.1
	"The purpose of clinical evaluation is to assess the safety and effectiveness of an endovascular system. This evaluation is not intended to demonstrate the long-term performance of the prosthesis."		25539-1 8.7.1

Topic	Definition or Recommendation	Technology	References
	"The purpose of clinical evaluation is to assess the safety and effectiveness of a stent system. This evaluation is not intended to demonstrate the long-term performance of the stent."		25539-2 8.7.1
Specific aims	"Specific aims of the study shall be based on an appropriate risk assessment for the vascular prosthesis and shall be stated in the protocol. The specific aims can include the following. a) Evaluate the effectiveness of the vascular prosthesis, such as the 1) structural and material integrity of the prosthesis over time, 2) patency of the prosthesis over time, and 3) failure modes; b) Evaluate the safety of the vascular prosthesis, such as the adverse events."		ISO 7198 10.1.2
	Specific aims of the study shall be stated and can include the following, as appropriate: a) evaluation of the ability to position the DCP at the target location; b) verification of the ability of the DCP to be consistently, accurately, and safely brought into contact with the intended anatomic treatment site; c) evaluation of the acute (less than 24 h), sub-acute (24 h to 7 days), and chronic (more than 7 days) position of the DCP of the VDDCP, if applicable; d) evaluation of the acute (less than 24 h), sub-acute (24 h to 7 days), and chronic (more than 7 days) structural integrity and functionality of the VDDCP, if applicable; e) monitoring of local and systemic drug effects (over time);		ISO 12417 7.3.2

Topic	Definition or Recommendation	Technology	References
	f) evaluation of any explants; g) evaluation of the pathology of any pertinent tissues/organs; h) recording of adverse events, VDDCP failure modes, and VDDCP effects.		
	The specific objectives of the study shall be stated and can include the following, which are relevant for absorbable cardiovascular implants, as appropriate: a) evaluation of the position, structural integrity and functionality of the implant immediately after placement (and withdrawal, if interventionally placed) as well as at clinically relevant time points and during intermediate and advanced degradation; b) monitoring of local and systemic effects (over time) due to degradation of the material; c) comparison of the absorbable cardiovascular implant to current clinical best practice, in the form of a non-inferiority study or a superiority study against an appropriate comparator		ISO 17137 5.7.2
	a) evaluate the effectiveness of the endovascular system, such as the following: 1) ability to access the target location with the delivery system; 2) accuracy of deployment; 3) ability to withdraw the delivery system; 4) position, structural and material integrity and functionality of the prosthesis acutely and over time; 5) lesion characteristics (e.g. aneurysm size, restenosis, false lumen perfusion) over time; 6) device effects of failure (see Annex B for potential effects of failure);		ISO 25539-1 8.7.2

Topic	Definition or Recommendation	Technology	References
	b) evaluate the safety of the endovascular system, such as the following: 1) clinical effects of failure (see Annex B for potential clinical effects of failure); 2) adverse events.		
	a) Evaluate the effectiveness of the stent system, such as the: 1) ability to access the target location with the delivery system; 2) handling and visualization of the delivery system and visualization of the stent; 3) accuracy of deployment; 4) ability to withdraw the delivery system; 5) position, structural integrity and functionality (e.g. patency, freedom from target lesion revascularization) of the stent acutely and over time; 6) lesion characteristics (e.g. restenosis, aortic false lumen perfusion) over time; 7) device effects of failure (see Annex C for potential device effects of failure); b) Evaluate the safety of the stent system, such as the: 1) clinical effects of failure (see Annex B for potential clinical effects of failure); 2) adverse events.		ISO 25539-2 8.7.2
	"The clinical investigation programme shall be designed to provide substantial evidence of acceptable safety and effectiveness to support the intended labelling for the device."		ISO 5840-2 7.4.1

Topic	Definition or Recommendation	Technology	References
			ISO 5840-3 7.4.1
Methodological requirements	"For clinical investigations to serve as a basis for market approval, there should be sufficient data to support safety and effectiveness. These studies should include a statistical methodology, specific inclusion/exclusion criteria, use of accepted endpoint definitions, a rigorous method of collecting information on defined case report forms, a rigorous system to monitor the data collection, defined follow-up intervals, and complete follow-up of the study populations"		ISO 5840-2 7.4.1 ISO 5840-3 7.4.1 ISO 5910 7.4.1
Population			
	See appropriate study design/ objectives: "The clinical investigation shall be designed to evaluate whether the investigational device is suitable for the purpose(s) and the population(s) for which it is intended" CIP: Inclusion and exclusion criteria for subjects have to be described		ISO 14155 6.3
External validity	To describe in CIP: relationship between the study population and the target population		ISO 14155 A.6.3
	"Study populations shall be representative of the intended post-market patient population, including aetiology and pathology."		ISO 5840-2 7.4.2

Topic	Definition or Recommendation	Technology	References
			ISO 5840-3 7.4.2 ISO 5190 7.4.2.1
Characteristics of investigational sites	"The sponsor shall identify criteria necessary for the successful conduct of the clinical investigation prior to start of the site qualification process, including the facilities required at the clinical investigation site, principal investigator's qualification and the type of environment (e.g. hospital versus home-based)." "Prior to the initiation of the clinical investigation, the qualifications of the principal investigator(s) and adequacy of the investigation site(s) shall be verified and documented in an investigation site selection report. The rationale for selecting an investigation site shall be documented."		ISO 14155 6.8
External validity	"The investigation site's facilities should be similar to the facilities required for the intended use of the investigational device(s), although additional equipment and capabilities may be needed at investigation sites during the clinical investigation to ensure that the necessary safety precautions are available."		ISO 14155 6.8
Characteristics of investigational sites	Pivotal studies: "Clinical investigations shall be conducted in institutions with appropriate facilities, case-load and case-mix and by investigators with appropriate experience, skills and training. Emphasis should be placed on the multidisciplinary heart team approach*. Clinical investigations shall be designed to include enough subjects, investigators, and institutions to be representative of the intended patient and user populations to provide generalizable		ISO 5840-2 7.4.5 ISO 5840-3 7.4.5

Topic	Definition or Recommendation	Technology	References
	results. ** The design should include consideration of and justification for such aspects as disease aetiology, disease severity, gender, age (e.g. adult, paediatric) and other special patient populations as appropriate…. Consideration and justification should also be made to account for any expected differences in standard of care or patient outcomes based upon the geographic distribution of the intended patient or user populations." *Additionally, to the other text in ISO 5840-3 and ISO 5910, ** additionally in ISO 5910		ISO 5910 7.4.5
Selection criteria for sites	"a) suitable distribution of sites; b) access to the defined patient population; c) presence of a local or central institutional review board (IRB)/ethics committee (EC); d) qualified centres, following the guidelines on operator and institutional requirements;* published jointly by the professional societies (see Reference [26]);*** published jointly by the Society for Cardiovascular Angiography and Interventions (SCAI), the American Association for Thoracic Surgery (AATS), the American College of Cardiology (ACC) and the Society for Thoracic Surgeons (STS) (See Reference [6], [13], [40], [41]); e) expert imaging with accredited operators and facilities (see ISO 5840-1:2021, Annex G);** Annex H instead of Annex G *** Annex R instead of Annex G f) appropriate study coordinator and other administrative staff associated with data collection or coordination of the study; g) adequate resources (e.g. facilities and equipment, security and storage, working space for monitor and additional equipment);		ISO 5840-2 7.4.5 ISO 5840-3 7.4.5 ISO 5910 7.4.5

Topic	Definition or Recommendation	Technology	References
	h) accordance with good clinical practice (GCP), including but not limited to: regulatory agency and IRB/EC approval prior to study initiation; proper consenting of all research subjects; CIP adherence, with any deviation properly approved or documented; proper adverse event reporting; and, adequate device accountability; i) experience with clinical investigations; j) acceptable results of previous regulatory inspections” * e) involvement of a multi-disciplinary heart team in patient selection including at least one non-conflicted physician *** e) involvement of a multi-disciplinary heart team in patient selection; * additionally in ISO 5840-3 ** alternatively in ISO 5840-3 ***additionally in ISO 5910		
Selection criteria for clinical investigators	a) qualifications by education, training (by manufacturer or medical experts), relevant experience, and meeting all applicable regulatory requirements; b) motivation to continue patient recruitment and to undertake long-term accurate follow-up; c) prior clinical research experience;* in the relevant area d) avoidance of competing studies (e.g. to avoid selection, channelling biases); e) minimising potential conflict of interest; if there are substantial conflicts of interest with the manufacturer, such conflicts shall be managed, which should involve (but not necessarily		ISO 5840-2 7.4.5 ISO 5840-3 7.4.5 ISO 5910 7.4.5

Topic	Definition or Recommendation	Technology	References
	be limited to) consideration of the use of a non-conflicted physician for patient recruitment, informed consent, and reporting (see References [6] and [8]). *d) enrolment history in previous related studies * additionally in ISO 5910		
Patient selection criteria	"The intended patient population shall be specified and any salient differences between the intended population and those studied shall be justified. The study should only include patients who are willing and able to participate in the follow-up requirements."		ISO 5840-2 7.4.7 ISO 5840-3 7.4.7 ISO 5910 7.4.7
	Inclusion criteria to consider to ensure that the expected benefit of treatment outweighs the risk to subjects: "a) patient demographics (e.g. age, gender, ethnicity*); b) disease aetiology (e.g. stenosis, primary or secondary regurgitation); c) severity of valve disease; d) symptomatic versus asymptomatic patients; e) predicted risk of surgical morbidity or mortality (e.g. STS Score, EuroSCORE II); f) co-morbid conditions (e.g. myocardial infarction, other valve disease, coronary or peripheral artery disease, atrial septal defect, patent foramen ovale, previous infective endocarditis, rheumatic heart disease, degenerative neurological disorders, frailty, previous cardiac		ISO 5840-2 7.4.7 ISO 5840-2 7.4.7 ISO 5910 7.4.7

Topic	Definition or Recommendation	Technology	References
	interventions, prior stroke or systemic embolism, chronic kidney disease, hematologic disorders, chronic lung disease); g) ventricular function and chamber size (e.g. ejection fraction, systolic/diastolic dimension or volumes); h) haemodynamic stability (e.g. mechanical circulatory assist devices, inotropic support); i) surgical status (e.g. elective, urgent, emergency, salvage); j) tolerance for procedural/post-procedural anticoagulation or antiplatelet regimens; k) life expectancy; l) device/procedure specific anatomical considerations (e.g. valve size, calcification, congenital abnormalities, access site conditions, device placement location, ability to tolerate TEE); m) potential patient prosthesis mismatch;** n) access to sufficient follow up treatment (all types of physical and medicinal therapy). *Additionally in ISO 5910, ** missing in ISO 5910		
	Population not mentioned, but reference to ISO 12417-1 regarding target population		ISO 17137
	Not mentioned except “Patient inclusion and exclusion criteria shall be clearly identified		ISO 7198
	“Patient inclusion* and exclusion criteria shall be clearly identified. The criteria shall specify the target population (i.e. those for whom the implant is intended) and the accessible population (i.e. those who agree and are able to participate fully in the study).”		ISO 25539-1 8.7.3

Topic	Definition or Recommendation	Technology	References
	"Patient selection and exclusion criteria shall be clearly established. The criteria shall specify the target population (i.e. those for whom the VDDCP is intended) and the accessible population (i.e. those who agree to participate fully in the study)."		ISO 25539-2 8.7.3 ISO 12417-1 7.2.3
Prognostic factors	Under "Clinical data requirements" the section 7.4.9.2 Baseline data lists characteristics to collect, that are mainly prognostic factors or diagnostic data needed for the intervention. The list under 7.4.9.3 Peri-procedure data also contains several prognostic factors besides data to document the intervention. "If any of the [listed] data are deemed not applicable, a justification shall be provided."		ISO 5840-2 7.4.9
	Under "Clinical data requirements" the section 7.4.8.2 Baseline data lists characteristics to collect, that are mainly prognostic factors or diagnostic data needed for the intervention. The list under 7.4.8.3 Peri-procedure data also contains several prognostic factors besides data to document the intervention. "If any of the [listed] data are deemed not applicable, a justification shall be provided."		5910 7.4.8.2 7.4.8.3
	Under "Data acquisition" the section 10.1.4 pre-operative data lists characteristics to collect, that are mainly prognostic factors or diagnostic data needed for the intervention. The list under 10.1.4 operative data also contains several prognostic factors besides data to document the intervention.		ISO 7198 10.1.4
	Under "Data acquisition" the section 7.3.4 pre-operative data lists characteristics to collect, that are mainly prognostic factors or diagnostic data needed for the intervention. The list under 7.3.4 operative data also contains several prognostic factors besides data to document the intervention.		?

Topic	Definition or Recommendation	Technology	References
	Under “Data acquisition” the section 8.7.4 pre-operative data lists characteristics to collect, that are mainly prognostic factors or diagnostic data needed for the intervention. The list under 8.7.4 operative data also contains several prognostic factors besides data to document the intervention.		25539-1 8.7.4
Sample size	See “statistical methods”		
Intervention			
Definition of intervention	CIP requirements: “a) Summary description of the investigational device. b) Details concerning the manufacturer of the investigational device. c) Name or number of the model/type, including software version and accessories, if any, to permit full identification. d) Description as to how traceability shall be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers, or serial numbers. e) Intended purpose of the investigational device in the proposed clinical investigation. f) The populations and indications for which the investigational device is intended. g) Description of the investigational device, including any materials, that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.		ISO 14155 A.2

Topic	Definition or Recommendation	Technology	References
	h) Summary of the necessary training and experience needed to use the investigational device based on risk assessment. i) Description of the specific medical or surgical procedures involved in the use of the investigational device. j) References to the IB and IFU. The above information shall also be provided as far as available for the comparator, if applicable"		
Definition/ description of intervention	IB requirements: a) Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device. b) Statement concerning the regulatory classification of the investigational device, if relevant. c) General description of the investigational device and its components, including any materials used, and details on those that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human, or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations. d) Summary of relevant manufacturing processes and related validation processes, to demonstrate that the investigational devices are manufactured and verified under a controlled process according to the applicable regulations. e) Description of the mechanism of action of the investigational device, along with supporting scientific literature.	ISO 14155 B.2	

Topic	Definition or Recommendation	Technology	References
	f) Manufacturer's instructions for installation, maintenance of hygienic conditions and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant. g) Sample of the label, for example sticker or copy, and instructions for use or reference to, and information on any training required. h) Description of the intended clinical performance		
Device modification /IB	In case of an investigational device design change that can occur during the course of the clinical investigation, the IB shall be updated and provide a justification for the change including an update of the risk management section of the IB, if required.	All MD (except IVD)	ISO 14155 6.5
Definition/ description	In the chapters on requirements for study protocol considerations and the final report no description of the intervention (investigational device and related procedure) is mentioned. Only under 'data acquisition' under procedural data or operative data respectively, identification data for the device, the procedure and relevant medications are listed.		ISO 25539-1 ISO 25539-2 8.7.4 7198 9.1.4 12417-1 7.3.4
	No requirement of a definition and description of the intervention in the study protocol is stated. Under "7.4.9 or 7.4.8 respectively, clinical data requirements", 7.4.9.3 peri-procedure data a detailed list of issues to describe the intervention is provided. "If not all data are deemed applicable, a justification shall be provided".		5840-2 7.4.9 5840-3

Topic	Definition or Recommendation	Technology	References
			7.4.9 5910 7.4.8
Co-medication	Refers in general to ISO 14155 and ISO 12417-1 in case of a drug-eluting device for requirements of CIP and for the final report. "The following data may be particularly relevant for absorbable implants and shall be recorded for each patient in the study: a) Relevant medications taken prior to and post-surgery, such as antithrombotics or antibiotics, during the hospital stay, and prescribed at discharge. Because there can be some unanticipated interactions between the absorbable implant and pre- or post-operative medications, especially those that include an API, consider capturing all medications."		17137 5.7.4
Contextual factors in general			
User dependency/ learning curve/RM	"Where the risk management report's conclusions require training on the investigational device, consideration should be made by the sponsor about the extent of the training (e.g. animal model, cadaver training, support to users throughout the clinical investigation)." See RM rec #	All MD (except IVD)	ISO 14155 6.2.2
User dependency/ learning curve	"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."		ISO 5840-2 7.4.5 ISO 5840-3 7.4.5

Topic	Definition or Recommendation	Technology	References
			ISO 5910 7.4.5
	Not mentioned in ISO 7198, ISO 12417-1, ISO 17137, ISO 25539-1, ISO 25539-2		
Quality control	?		
Comparator			
Choice of comparator	See appropriate study design/ objectives 6.3 " the results of the clinical evaluation… serve to justify the choice of control group(s) and if applicable, comparator(s),		ISO 14155 6.3
	See also Risk management benefit-risk analysis: An important consideration is whether an anticipated benefit can be achieved through the use of alternative solutions without that risk or with smaller risk. This involves comparing the residual risk for the manufacturer's medical device with the residual risk for similar medical devices."		ISO 24791 7.4.1
	As rationale for a RCT: "a) ethical considerations may require a head-to-head comparison with alternative treatments or standard of care;"		ISO 5840-2 7.4.1 ISO 5840-3 7.4.1 ISO 5910 7.4.1
	Definition: "active comparator, active control intervention generally accepted or demonstrated to be safe and effective for the condition of interest that can be used as a basis		ISO 5910 3.3

Topic	Definition or Recommendation	Technology	References
	of comparison of the safety and effectiveness of the heart valve repair device. Note 1 to entry: The active comparator is generally the standard of care for the condition."		
	"The CIP should identify and include an appropriate comparator or control. A randomized trial powered for detection of differences with an existing control device is recommended. Control devices should be contemporary non-absorbable devices, unless absorbable devices have been established as the preferred mode of treatment in the intended clinical application."		ISO 17137 5.7.3
	For novel devices (they "include devices with characteristics … that have never been evaluated before"): "If a comparable device is on the market, the study control may be the comparable device or another comparator, such as non-surgical therapy. If a comparable device is not on the market, randomisation against an appropriate comparator should be used.		ISO 5840-2 7.4.6.3
	"The use of objective performance criteria (OPC) is the recommended method for the statistical evaluation of adverse event data for new devices based on established device designs"		ISO 5840-2 7.4.6.2
	"If a comparable device is on the market, the study control may be the comparable device or another active comparator, such as surgery or medical therapy. If a comparable device is not on the market, randomisation against an appropriate active comparator with established clinical history should be used."		ISO 5840-3 7.4.6. ISO 5910 7.4.6
	"A control should be included in the study to appropriately address the questions postulated. If an appropriate control is not or cannot be identified, or if a concurrent control is unnecessary, a method		ISO 7198 10.1.3 ISO 25539-1

Topic	Definition or Recommendation	Technology	References
	for evaluating the clinical outcomes shall be prospectively defined and justified (e.g. through use of a performance goal)."		8.7.3 ISO 25539-2 8.7.3
	"If an appropriate control is not, or cannot be identified, or a concurrent control is unnecessary, a method for evaluating the clinical outcomes shall be prospectively defined and justified. The control should be appropriate to the questions being addressed in the study."		ISO 12417-1 7.3.3 ISO 17137 5.7.3
	The final report shall include the following: … b) rationale, based on risk assessment and questions to be answered, for selection of the following: …choice of control; …"		ISO 7198 10.1.5
	"The final report shall include, at a minimum, the following:…c) justification for selection of the following: … choice of control…"		ISO 12471 7.3.5
	"The clinical report shall include the following: … b) rationale, based on risk assessment and questions to be answered, for selection of the following: …choice of control; …"		ISO 25539-1 8.7.5
No comparator	CIP "Absence of controls shall be justified"		ISO 14155 A.6.1
Outcome			
Definitions Endpoint	"<primary> principal indicator(s) used for providing the evidence for clinical performance (3.11), effectiveness (3.20) or safety in a clinical investigation (3.8)."		ISO 14155 3.22

Topic	Definition or Recommendation	Technology	References
	"Note 1 to entry: The primary hypothesis is formulated based on the pre-defined primary endpoint (3.22) and is usually used to calculate the sample size."		3.25
	"<secondary> indicator(s) used for assessing the secondary objectives (3.37) of a clinical investigation (3.8)"		ISO 14155 3.23
Relation to objectives	"The objectives of the clinical investigation shall translate directly into the pre-specification and operationalisation of the primary endpoint(s). "		ISO 14155 Annex A5
Which endpoints	"The primary endpoint shall be appropriate for the investigational device and should be clinically relevant."		ISO 14155 Annex A6.1 c
	"NOTE Composite endpoint is a pre-specified combination of more than one endpoint and can be used cautiously by including only components that have relatively equal clinical importance, frequency, and anticipated response to the presumed mechanism of action."		ISO 14155 Annex A6.1 c
Which outcomes	"The benefit arising from a medical device is related to the likelihood and extent of improvement of health expected from its use. Benefits can be described in terms of positive impact on clinical outcome, the patient's quality of life, outcomes related to diagnosis, positive impact from diagnostic devices on clinical outcomes, or a positive impact on public health. The nature and degree of benefits can depend on the patient population." (see #Rec y General design issues)	All MD	ISO 24791 7.4

Topic	Definition or Recommendation	Technology	References
	ISO 17137 on absorbable stents refers to ISO 14155 and on ISO 12417-1 (drug-eluting stents) generally for design issues and also with regard which data to collect, and to report		ISO 17137 5.7.1; 5.7.4; 5.7.5
	"Definitions of success and failure for each endpoint and the duration of follow-up needed to assess each endpoint shall be specified. A definition for the study success shall also be specified (e.g. meeting both the safety and effectiveness primary endpoints)."		25539-1 8.7.3
Appropriate endpoints	"The clinical investigation endpoints need to include both safety and effectiveness endpoints. The ability to compare clinical investigations and to create useful observational registries requires the use of consensus definitions of endpoint components, particularly when comparing transcatheter valve outcomes to surgical valve outcomes." "The clinical investigation shall follow the most recent guidelines for safety and performance or effectiveness endpoints (see Reference [14])."		ISO 5840-1 Annex L.1, L2.1
Appropriate endpoints	For clinical investigations to serve as a basis for market approval accepted endpoint definitions should be used. Safety and effectiveness endpoints shall be specified in the CIP. "The CIP shall clearly define the objectives of the study and specify safety and effectiveness endpoints. The CIP shall specify all anticipated study-related adverse events, including device and/or procedure-related adverse events, in accordance with Annex J and published definitions. The definitions of the outcome measures should be consistent with those described in this document to allow comparability of heart valve systems."		5840-2 7.4.2 5840-3 7.4.2

Topic	Definition or Recommendation	Technology	References
	"The ability to compare clinical investigations and to create useful observational registries requires the use of standardized definitions of endpoint components."		5910 Annex S1
	"The CIP shall specify safety and effectiveness endpoints (see Annex S), linked to study success criteria. The CIP shall specify study-related adverse events, including device and/or procedure-related adverse events in accordance with Annex Q and published definitions. The definitions of the outcome measures should be consistent with those employed in previous studies of heart valve repair devices, when appropriate."		5910 7.4.2
	"The choice and timing of primary and secondary study endpoints shall be driven by the study objectives, the disease, the patient population, the technology, the post-operative medical treatment (e.g. heart failure treatment, antithrombotic medication) and anticipated risks. Endpoints shall include safety and effectiveness such as time-related valve safety, quality of life, symptomatic and functional status, and device and procedural success. Other tertiary or descriptive endpoints should be considered relative to the technology. Further suggestions for clinical investigation endpoint selection and timing for transcatheter heart valve systems are provided in ISO 5840-1:2021, *Annex L **Annex S *ISO 5840-3 ** ISO 5910		5840-2 7.4.3 5840-3 7.4.3 5910 7.4.3
	"A specific question or set of questions (i.e. hypotheses) shall be defined prospectively. These questions shall delineate the appropriate primary safety and effectiveness endpoints to be evaluated. Definitions of success and failure for each endpoint and the duration of follow-up needed to assess each endpoint		7198 10.1.3

Topic	Definition or Recommendation	Technology	References
	shall be specified. A definition for the study success shall also be specified (e.g. meeting both the safety and effectiveness primary endpoints)."		
	"A specific question or set of questions shall be defined prospectively. These questions shall delineate the appropriate end points to be measured. Definitions of success and failure shall also be prospectively defined for all primary and any secondary end points where statistical analyses (other than presentation of descriptive statistics) will be used to support marketing approval." "In addition, the way in which the success of the entire study will be determined shall be prospectively defined. The definitions of success and failure shall incorporate quantitative values specifically applicable to the imaging modalities or other evaluation techniques to be used in the study."		12417-1 7.3.3
	"The CIP shall identify the critical data points and end points for the study. Definitions of success and failure shall also be prospectively defined for all primary and any secondary end points where statistical analysis (and presentation of descriptive statistics) will be used to support marketing approval."		17137 5.7.3
	"A specific question or set of questions (i.e. hypotheses) shall be defined prospectively. These questions shall delineate the appropriate safety (e.g. freedom from major adverse events), effectiveness (e.g. technical success in absence of serious device related events) or combined safety and effectiveness endpoints (e.g. 30-day mortality for the treatment of dissections) to be measured. Definitions of success and failure for each endpoint and the duration of follow-up needed to assess each endpoint shall be specified."		25539-1 8.7.3 25539-2 8.7.3

Topic	Definition or Recommendation	Technology	References
/secondary endpoints	"Definitions, primary and secondary clinical endpoints, measurement methods and data analysis shall be specified in the clinical protocol. Secondary endpoints might include the following: — individual components that make up any composite primary endpoints; — technical success [e.g. successful placement of all endovascular graft components at the intended implantation site(s) with patency and an absence of significant device deformations, e.g. kinks, stent eversion, twists]; — procedural success (e.g. technical success in absence of serious device-related adverse events at 30 d); — device and clinical effects of failure; — secondary endovascular procedures; — conversions to open surgical repair; — indication-related mortality (e.g. aneurysm-related mortality); — longer-term outcomes (e.g. 12-month safety data if the primary safety endpoint is at 30 d)."		25539-1 8.7.3
	Definitions of primary effectiveness (e.g. primary patency), primary safety (e.g. freedom from major adverse events) and secondary clinical end points, measurement methods, and data analysis shall be specified in the clinical protocol. Secondary end points might include the following: — individual components that make up any composite primary end points;		25539-2 8.7.3

Topic	Definition or Recommendation	Technology	References
	— change in quality of life status or other relevant patient reported outcomes; — measure of therapeutic success (e.g. ankle brachial index); — technical success [e.g. successful placement of all stents at the intended implantation site(s) with patency]; — procedural success (e.g. technical success in absence of serious device-related adverse events at 30 days); — device and clinical effects of failure; — repeat procedures (e.g. target vessel revascularization); — longer-term outcomes (e.g. 12-month safety data if the primary safety end point is at 30 days).Fcore lab		
Appropriate endpoints	Under “data acquisition “under ‘operative data’, post-operative data safety and effectiveness endpoints are listed. The list is characterised as a minimum of data that should be recorded for each patient in the study		7198 10.1.4
	Under “data acquisition “under ‘operative data’, post-operative data safety and effectiveness endpoints are listed. Reference to Annex A for definitions of potential clinical events. The list is characterised as a minimum of data that should be recorded for each patient in the study		12417-1 7.3.4
	Refers to ISO 12417-1 for guidance on endpoints among other issues.		17137 5.7.3
	Under “data acquisition “under ‘operative data’, follow-up data safety and effectiveness endpoints are listed. The list is characterised as a minimum of data that should be recorded for each patient in the study		25539-1 8.7.4

Topic	Definition or Recommendation	Technology	References
	Under “data acquisition “under ‘procedural data’, ‘follow-up data” safety and effectiveness endpoints are listed. The list is characterised as a minimum of data that should be recorded for each patient in the study		25539-2 8.7.4
See “specific aims” above	Provides categories of outcomes for effectiveness and safety		7198, 12417, 17137, 25539-1, 25539-2
Duration of Follow-up	“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 might have a shorter time for the primary endpoint that a younger, healthier population.”		5840-1 Annex L.5
Definition safety endpoints	Safety “freedom from unacceptable risk”		ISO 14971 3.26
	Risk “combination of the probability of occurrence of harm… and the severity of that harm.”		ISO 14971 3.18
	Harm ”injury or damage to the health of people, or damage to property or the environment”		ISO 14971 3.3
	“Adverse event AE untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects …, users or other persons,		ISO 14155 3.2

Topic	Definition or Recommendation	Technology	References
	whether or not related to the investigational medical device … and whether anticipated or unanticipated. Note 1 to entry: This definition includes events related to the investigational medical device or the comparator (3.12). Note 2 to entry: This definition includes events related to the procedures involved. Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators."		
	"adverse device effect ADE adverse event (3.2) related to the use of an investigational medical device (3.34) Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction (3.33) of the investigational medical device. Note 2 to entry: This definition includes any event resulting from use error (3.53) or from intentional misuse of the investigational medical device. Note 3 to entry: This includes 'comparator' (3.12) if the comparator is a medical device."		ISO 14155 3.1
	"serious adverse event SAE adverse event (3.2) that led to any of the following a) death, b) serious deterioration in the health of the subject (3.50), users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function including chronic diseases, or		ISO 14155 3.45

Topic	Definition or Recommendation	Technology	References
	3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP (3.9), without serious deterioration in health, is not considered a serious adverse event.		
	"serious adverse device effect SADE adverse device effect (3.1) that has resulted in any of the consequences characteristic of a serious adverse event (3.45)"		ISO 14155 3.44
	"serious health threat signal from any adverse event or device deficiency (3.19) that indicates an imminent risk of death or a serious deterioration in the health in subjects (3.50), users or other persons, and that requires prompt remedial action for other subjects, users or other persons Note 1 to entry: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals."		ISO 14155 3.46
Adverse events, data collection	"The manufacturer shall ensure the following information is documented on a CRF, for all observed AEs: — date of onset or first observation; — description of the event;		5840-2 Annex J3

Topic	Definition or Recommendation	Technology	References
	— seriousness of the event; — presumptive causal relationship of the event to the device, procedure or patient condition; — treatment required; — outcome or status of the event.”		
Adverse events, definitions	“Each AE shall be defined and categorised as either a serious adverse event (SAE) or non-serious adverse event according to the definitions in ISO 14155:2020.” Definitions of ISO 14155 apply with regard to ADE and device deficiencies		5840-2 Annex J4, J5, J6 5910 Annex Q4, Q5, Q6
	“Anticipated adverse events identified via the risk analysis shall be clearly specified in the CIP prior to the initiation of the study. Unanticipated adverse events shall be recorded as such and the causality appropriately adjudicated.”		5840-2 Annex J8.1 5840-3 Annex G8.1 5910 Annex Q.8.1
Composite endpoints	“It is also important that composite endpoints which combine clinical safety and effectiveness are avoided, because the individual components of safety and effectiveness may move in opposite directions.”		5840-2 Annex J8.1 5840-3 Annex G8.1

Topic	Definition or Recommendation	Technology	References
			5910 Annex Q.8.1
Classification of AE	"For the incidence of AEs to be compared between heart valve replacement systems* [between heart valve repair devices and surgical valve repair] in randomized trials, it is important that the same definitions and methods of data collection are used in both groups." *ISO 5840-2, ISO 5840-3 ** ISO 5910		5840-2 Annex J8.1 5840-3 Annex G8.1 5910 Annex Q.8.1
	"The most recent definitions* of specific adverse events shall be used for data collection on events related to the implantation procedure and the peri-procedural period, and AEs shall be reported as a simple percentage for the first 30 d." * for ISO 5840-3 MVARC and VARC are given as examples.		5840-2 Annex J8.1 5840-3 Annex G8.1 5910 Annex Q.8.1
	"For long-term follow-up beyond 30 d, linearized rates (events per 100 patients/years) and Kaplan-Meier actuarial analysis shall be used (see Reference [5]) for reporting adverse events." "For long-term follow-up beyond 30 d, linearized rates (events per 100 patients/years) and Kaplan-Meier actuarial analysis shall be used (see Reference [12]) for reporting adverse events."		5840-2 Annex J8.1 5840-3 Annex G8.1 5910 Annex Q.8.1

Topic	Definition or Recommendation	Technology	References
	"For long-term follow-up beyond 30 d, linearized rates (events per 100 patient/years) and Kaplan-Meier actuarial analysis shall be used (see Reference [9]) for reporting adverse events."		
	"Potential adverse events identified by the risk analysis that are not included in the published guidelines should be defined based on relevant/contemporary references"		5840-2 Annex J8.1 5840-3 Annex G8.1 5910 Annex Q.8.1
	45 examples of AE in 6 categories (events associated with surgical access, events associated with left ventricular apex access, events associated with cardiac damage, events associated with implant procedure, events associated with other organ damage, potential device related events) are listed that shall be reported. The list is not intended to be exhaustive, "but representative of adverse events with surgical heart valves". Further comments and recommendations on the quantification of bleeding and blood loss during and after surgery are given. 50 examples of AE in 6 categories (events associated with vascular access, events associated with left ventricular apex access, events associated with cardiac damage, events associated with implant procedure, events associated with organ damage, potential device related events) are listed. The list is not intended to be exhaustive, "but representative of adverse events with transcatheter heart valves".		5840-2 Annex J8.2 5840-3 Annex G8.2 5910 Q8.2

Topic	Definition or Recommendation	Technology	References
	47 examples of AE in 6 categories (events associated with vascular access, events associated with left ventricular apex access, events associated with cardiac damage, events associated with repair procedure, events associated with organ damage, potential device related events) are listed that shall be reported. The list is not intended to be exhaustive, "but representative of adverse events with heart valve repair systems".		
	G9 especially considers the case of RCTs when "transcatheter valve replacement is compared to surgical valve repair are compared. "The same definitions of adverse events shall be applied to both arms of the trial. However, the types of complications that could occur with catheter-based and surgical valve procedures may differ, though their impact on morbidity and mortality may be equally important. For procedure-related adverse events, it is necessary to compare a composite of access-related events."7 examples are given for surgically replaced valves. and comments and recommendations on the quantification of bleeding and blood loss during and after surgery are given. "To avoid bias in reporting of events in randomised trials, first time transcatheter valve replacement shall be compared to first time surgical valve replacement without concomitant procedures such as CABG or valve repair or replacement at another site."		5840-3 Annex G9
	Q9 especially considers the case of RCTs when "non-surgical valve repair is compared to surgical valve repair, the same definitions of adverse events shall be applied to both arms of the trial. However, the types of complications that could occur with catheter-based and surgical valve procedures may differ, though their impact on morbidity and mortality may be equally important. For procedure-related adverse events, it will be necessary to compare a composite of access-related events, ranking their severity by clinical outcomes." 7 examples		5910 Q9

Topic	Definition or Recommendation	Technology	References
	of AE associated with access for surgical repair and comments and recommendations on the quantification of bleeding and blood loss during and after surgery are given. "To avoid bias in reporting of events in randomized trials, first time non-surgical valve repair shall be compared to first time surgical valve repair without concomitant procedures such as CABG or valve repair or replacement at another site."		
	Annex A of ISO 12417-1 provides Table A.1 (4 pages) with definitions of potential clinical events such as aneurysm, thrombosis etc. in alphabetical order. Table A.2 lists definitions of potential technical events such as access failure		12417-1 Annex A
	Annex B (informative) provides Table B.1 (2 pages) with definitions of clinical effects of device failure such as aneurysm enlargement, thrombosis etc. in alphabetical order. Table B.2 lists definitions of device effects of failure such as access failure		25539-1 Annex B
Late AE	"It has been reported in literature that late adverse events can occur during the clinical evaluation of absorbable devices…. According to current knowledge, there is no in vitro test or in vivo animal study capable of predicting such a behaviour. Therefore, users should be cautious about the interpretation of preclinical data regarding the prediction of long-term clinical outcomes."		17137 5.7.1
AE classification severity ranking	"Outcomes of adverse events shall be assessed and classified according to severity (e.g. fatal, leaving permanent damage or disability, resolution without permanent damage)."As examples of clinical outcomes resulting from AE are listed: death, new or prolonged surgery, new or prolonged hospitalisation, permanent impairment of body structure or function, permanent pacemaker, required LVAD or transplant		5910 Q10

Topic	Definition or Recommendation	Technology	References
	"Potential clinical outcomes related to each adverse event identified shall be ranked by severity consistent with the CIP. Ranking the severities allows for meaningful comparisons among different studies, clinicians, cohorts, delivery techniques and devices. Clinical outcome severity rankings included in the CIP shall be based on the most current published version of the relevant guidelines."		
Device-related mortality	Consistent with the reporting guidelines (see Reference [5]), all device-related mortality shall be reported. Recommendations are given for distinguishing between device-related death and death by due to deteriorating myocardial function unrelated to the device.		5840-2 Annex J10 5840-3 Annex G10
Safety/ OPC	"If objective performance criteria (OPC)-based clinical study design is employed, methods of evaluating clinical data shall include comparing all late complications to the OPC."		5840-2 Annex I.1
	"Safety can be assessed over the defined timeframe by comparing the occurrence of late (>30 d post-implant) complications to objective performance criteria, OPC. The OPC are the average rates of valve-related complications as assessed by linearized occurrence rates. The values in Table I.1 may be used in the comparison, without further justification. The data in Table I.1 were derived using the same methodology as the original OPC, an analysis of safety and effectiveness data submitted by manufacturers in pursuit of premarket approval of bioprosthetic and mechanical valves (yielding 38359 follow-up years) combined with an analysis of recent literature from 1999 to 2012 (yielding 208585 follow-up years). There was no significant heterogeneity between the two sources of data, either in methods of data collection or in complication rates. See Reference [12]." AE listed in table I.1 "Objective performance criteria for surgical heart valve substitutes are Thromboembolism, valve		5840-2 Annex I.2

Topic	Definition or Recommendation	Technology	References
	thrombosis, major haemorrhage, major paravalvular leak, endocarditis, values are in percentage per valve-year See also statistical methods/ sample size.		
	"See ISO 5840-2:2021, Annex J and ISO 5840-3:2021, Annex H for adverse events. Additional safety endpoints should be considered based upon the patient population, the investigational design and the device. The following mortality endpoints shall be reported: — all-cause mortality; — cardiovascular mortality; — non-cardiovascular mortality; — procedural mortality (30 d from procedure or discharge from the hospital, whichever is longer); — device related mortality."		ISO 5840-1Annex L2.2
Definition of causal relationship of AE	"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." For each category a definition is provided.		5840-2 Annex J7 5840-3 Annex G7 5910 Annex Q7

Topic	Definition or Recommendation	Technology	References
	"In addition to establishing this causal relationship, the probability of relationship shall also be established by categorizing each AE as either definitely, possibly or not related to the device, procedure or patient condition." …or other cause.		
	"Reportable clinical events as defined by the protocol. Special care should be taken when adjudicating an adverse event to be non-implant related, since effects of either material degradation or API, or both, may be observed systemically or at sites distal to the implant site."		17137 5.7.4
Responsibility for evaluation of safety endpoints	"The sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall … review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device and procedures required by the CIP; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d), and e) given below, NOTE 1 Classification of adverse events and safety evaluation can be performed by an independent Clinical Events Committee (CEC) to mitigate the potential for bias and financial conflict." "The principal investigator shall … record every adverse event and observed device deficiency, together with an assessment (adverse event categorization),.."		ISO 14155 9.2.5 ISO 14155 10.8
Who evaluates AE	"An independent, multi-disciplinary committee of qualified experts shall adjudicate causality to assign the specific cause of an adverse event. Formal adjudication of adverse events is intended to manage the ambiguity and bias in assigning causality."		5840-2 Annex J7 5840-3 Annex G7

Topic	Definition or Recommendation	Technology	References
			5910 Annex Q7
Follow-up of AE	"Any SAE shall be followed until it has resolved or in the investigator's opinion it is no longer clinically relevant." *"The long-term outcome shall be reported, including permanent device-related impairment." *only in ISO 5840-2 and ISO 5840-3		5840-2 Annex J9 5840-3 Annex G10 5910 Annex Q11
Effectiveness endpoints	The normative Annex L lists clinical investigation endpoints for heart valve replacement devices. "Endpoints shall reflect patient centric benefit such as living longer, feeling better or functioning better. Endpoints reported at specific times shall be prespecified and justified. For comparison with other studies, it is recommended that endpoints are reported, at a minimum, at procedure, 30 d, between 3 months and 6 months, and at 1 year."		5840-1 Annex L.1
	"Effectiveness means that the device itself is conferring some clinical benefit but there is a spectrum of effectiveness which shall be quantified. The assessment of effectiveness shall incorporate an assessment of device performance because it is possible for patients to claim improved functional status due to concomitant changes in medication, a placebo effect or because they do not wish to disappoint their physician. All assessments of effectiveness should be based on physical examination with access to imaging, haemodynamic and other relevant data. All assessments should be carried out by independent, unconflicted physicians,		5840-1 Annex L.2.3

Topic	Definition or Recommendation	Technology	References
	where possible. In order to be considered effective, the device shall perform as intended without deleterious haemodynamic consequences, e.g. significant regurgitation." A list of 16 single outcome endpoints in the categories "immediate outcome (for transcatheter valves only)" and "outcome at 30 d and during long-term follow-up" is provided that shall be reported. If any of the endpoints is deemed not applicable, a justification shall be provided.		
	L.3 and S.2.4 respectively provide a definition for heart failure hospitalisation.		5840-1 L.3 5910 Q.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 major adverse cardiac events (MACE) should be specified/ defined because of the lack of universal agreement on the components of this safety endpoint." "The use of a single composite clinical safety and performance or effectiveness endpoint, especially when the individual components of safety and efficacy move in opposite directions, is not recommended. If a single composite clinical safety and performance or effectiveness endpoint is used, it is important to assess the individual components of the composite primary endpoint as secondary endpoints."		5840-1 Annex L.4
Effectiveness endpoints	Under "Clinical data requirements" the section "7.4.9.4 Follow-up data" besides AE lists performance / effectiveness outcomes. A justification has to be provided, if any of the listed variables are deemed not applicable.		5840-2 5840-3 7.4.9.4
Duration of Follow-up	"…, the CIP shall specify total duration of the study, including long-term patient follow-up which may continue in the post-market setting (see also 7.4.9.6)."		5840-2 7.4.6.1

Topic	Definition or Recommendation	Technology	References
	"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"		5910 7.4.6
	"The clinical investigation shall be continued for a minimum of 12 months for each patient unless a justification for a different study duration is provided."		7198
	"The duration of patient follow-up shall be determined in relation to the objectives of the clinical investigation. The duration of follow-up shall also take into account the effect of comorbidities on the life expectancy of the patient population."		12417-1 7.3.3 17137 5.7.3
	"The duration of patient follow-up for absorbable cardiovascular implants can differ from durable cardiovascular implants. In addition to meeting the objectives of the clinical investigation, the duration of the trial for an absorbable cardiovascular implant shall consider the expected duration of a) mechanical support or structural integrity of the implant, b) physical presence of the absorbable material or degradation products, and c) complete absorption.		17137 5.7.3

Topic	Definition or Recommendation	Technology	References
	Specifically, the clinical study duration should be guided by both bench and animal studies, and should be sufficient to capture clinical events at key time points during and potentially after complete implant degradation. Absorbable metal implants should emphasize the use of animal studies for determining clinical study duration, given the challenges with using bench studies for assessing degradation rates (see 5.5)."		
	"The clinical investigation shall be continued for a minimum of 12 mos for each patient unless a justification for a different study duration is provided." "Longer-term patient follow-up (e.g. 3 years to 5 years after the last prosthesis has been implanted) may be appropriate for the post-market clinical assessment of device designs with a limited history of clinical use."		25539-1 8.7.3
Follow-up intervals	"Follow-up data shall be collected at approximately 30 d, at least one specific time point between three months and six months, at one year, and at a minimum annually thereafter until the investigation is completed, as defined in the CIP."		5840-2 7.4.9.4
	"Patient follow-up intervals shall include a minimum of a baseline assessment at discharge and an assessment at the specified study duration. A justification will be required for follow-up intervals."		7198 10.1.3
	"Patient follow-up intervals shall include a minimum of a baseline assessment at discharge and at the end of the study. A justification shall be provided for timing of follow-up intervals."		12417-1
	"A justification shall be required for follow-up intervals but may be based on ether clinical end points or expected degradation times of interest, or both. The follow-up period shall be chosen to represent a realistic test of the performance of the implants and to allow any risks associated with adverse device effects to be identified and assessed. Selected intervals should		17137 5.7.3 5.7.5

Topic	Definition or Recommendation	Technology	References
	include the ability to assess the patient's response to loss of the implant's mechanical properties and generation of potentially elevated amounts of degradation products." "a rationale shall be provided for the selection of patient follow-up intervals and for the selection of assessments at each time point based on the degradation profile of the implant."		
	"Patient follow-up intervals shall include a minimum of a baseline assessment at discharge and an assessment at the specified study duration. A justification will be required for follow-up intervals."		25539-1
Completeness	"Whenever feasible, post-mortem examination and explant analysis is recommended to capture device related deaths and to ensure proper classification of adverse events. A high percentage of 'unknown cause of death' in any investigation of a new device is of serious concern."		5840-2 Annex J7 5840-3 Annex G7
Measurement of outcomes	"Echocardiography is the standard modality for the routine clinical assessment of replacement heart valves". Annex G provides an informative echocardiographic protocol with general requirements in G1 for facilities, personnel, a third party core lab, recording, archiving and reviewing imaging studies, intervals for echocardiography, imaging methodologies G.2 provides requirements for the modalities of echocardiographic studies and G.3 states that "A comprehensive study should be carried out describing all chambers and valves in addition to the replacement valve." It gives examples which information can be collected and lists indices for the characterisation of a replacement valve. G3.3 provides definitions of structural valve deterioration and what should be reported.		5840-1 Annex G
	"Consideration and appropriate justification should be made for the collection and analysis of site reported versus Core Lab adjudicated data."		5840-2 7.4.9.1

Topic	Definition or Recommendation	Technology	References
			5840-3 7.4.9.1 5910 7.4.8.1
	"Consideration should be given to the use of independent core laboratories and event adjudication committees, as appropriate. The sources of the data to be included in reporting (e.g. site, core lab, adjudication committee) should be specified in the protocol." Not in 25539-1 / 12471-1 and 17137		25539-2 8.7.3
	"The CIP shall include an explant pathology protocol with detailed instructions for evaluation by an independent cardiac pathologist (including operative or autopsy photographs) and instructions for the return of the explanted device to the manufacturer, where appropriate. Whenever feasible, the explanted device shall be subjected to appropriate functional, imaging and histopathological investigations. In the event of subject death, valuable information about implanted devices can be obtained by autopsy which should be encouraged whenever possible."		5910 7.4.8.1
Data analysis **RCT or general**			
Statistical methods/ description and justification	"With reference to A.5 [Objectives and hypotheses of the clinical investigation] and A.6,[Design of the clinical investigation] the description of and justification for statistical design and analysis of the clinical investigation shall cover the following:" (see below all issues under 14155 A.7)		14155 Annex A.7

Topic	Definition or Recommendation	Technology	References
	"Further or more specific information can be found in standards for different types of medical devices or in national regulations or guidance documents (see References [9], [10], [13])." Refers to FDA guidance on pivotal CI of medical devices 2013; FDA guidance on feasibility medical device studies, and on statistical guidance for CI of medical devices from MHRA 2017		
	CIP "The study design shall include a pre-specified statistical analysis plan and success criteria."		5840-2 7.4.2 5840-3 7.4.2 5919-7.4.2.1
Statistical methods/ selection and justification	"The manufacturer is responsible for selecting and justifying the specific statistical methodology used. The size, scope, and design of the clinical investigation shall be based on: a) the intended use of the device; b) the results of the risk analysis; c) the measures that will be evaluated; d) the expected clinical outcomes"		5840-2 7.4.6.1 5840-3 7.4.6 5910 7.4.6
A priori specification of statistical methods	"If a statistical analysis will be applied to the data to measure study success, an outline of the statistical-analysis plan shall be in place prior to initiating the study, and the detailed plan finalized prior to evaluating the study data. NOTE 1 See ISO 14155 for statistical considerations for the clinical investigation plan."		12417-1 7.3.3

Topic	Definition or Recommendation	Technology	References
	"Definitions, primary and secondary clinical endpoints, measurement methods and data analysis shall be specified in the clinical protocol.		25539-1 8.7.3 25539-2 8.7.3
Rationale for statistical methods	The final clinical report shall include the following: a) a study protocol… b) rationale, based on the risk assessment and questions to be answered, for selection of the following: 1) study size; 2) choice of control; 3) measurement methods; 4) statistical analyses employed; 5) patient follow-up intervals;…"		7198 10.1.5 25539-1 8.7.5 25539-2 8.7.5
	"The final report shall include, at a minimum, the following: …c) justification for selection of the following: 1) study size; 2) choice of control; 3) measurement methods; 4) statistical analyses employed; 5) patient follow-up intervals;"		12417-1 7.3.5
	"In addition to the final clinical investigation reporting of specifications outlined in ISO 14155 and ISO 12417-1, a rationale shall be provided for the selection of patient follow-up intervals and for the selection of assessments at each time point based on the degradation profile of the implant." Relevant here is the reference to ISO 14155 and 12417-1		17137 5.7.5
Statistical methods/ OPC	"The use of objective performance criteria (OPC) is the recommended method for the statistical evaluation of adverse event data for new devices based on established device designs."		5840-2 7.4.6.2 Annex I1, I2

Topic	Definition or Recommendation	Technology	References
	"If objective performance criteria (OPC)-based clinical study design is employed, methods of evaluating clinical data shall include comparing all late complications to the OPC." "Frequentist or Bayesian statistical methods may be used. The manufacturer is responsible for proposing and justifying the specific methodology used." "The formal statistical method applied to OPC specifies that the observed rates should be numerically less than twice the OPC."		
Definition of study success	"Pass/fail criteria to be applied to the results of the clinical investigation."		14155 Annex A.7g)
	See under "Endpoints/ appropriate endpoints" success criteria should be defined a priori		7198 12417-1 17137 25539-1 25539-2
	"The study design shall include a pre-specified statistical analysis plan and success criteria" see above		5840-2 7.4.2 5840-3 7.4.2 5919-7.4.2.1

Topic	Definition or Recommendation	Technology	References
Sample size calculation	"Sample size calculation and justification taking into account: 1) all relevant clinical data on outcome variable and effect size, if applicable; 2) assumptions of expected outcomes across treatment groups, if applicable; 3) adjustments due to any pre-planned interim analyses, if applicable; 4) detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable; 5) randomization allocation ratio (e.g. 1:1, 1:2), if applicable; 6) expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint). All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided. For exploratory and observational clinical investigations (see Annex I), in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size shall be provided."		14155 Annex A.7e)
Sample size	"For pivotal studies (single-arm or concurrent control), the sample size shall be justified and shall be sufficient to enable assessment of the study safety and performance or effectiveness endpoints of the surgical heart valve* transcatheter heart valve** system in the intended populations. Standard statistical methods shall be used to calculate the minimum sample size with prior specification of an appropriate Type 1 error rate and power. Sample size considerations shall also take into account the standard of care and available safety and		5840-2 7.4.6.1 5840-3 7.4.6

Topic	Definition or Recommendation	Technology	References
	performance or effectiveness data (including post-market or published data) on relevant therapies with similar intended use."		
	For pivotal studies (single-arm or concurrent control), the sample size shall be justified and shall be sufficient to enable assessment of the study safety and effectiveness endpoints of the heart valve repair device in the intended population. Standard statistical methods shall be used to calculate the minimum sample size with prior specification of a 5 % Type 1 error rate (one-sided). The statistical power, confidence intervals and effect sizes to be detected shall also be specified. Sample size considerations shall take into account the standard of care and available safety and effectiveness data (including post-market or published data) on relevant therapies with similar intended use		5910 7.4.6
Sample size and sample size calculation	"For a new heart valve repair device*[transcatheter heart valve system**], in a population with acceptable surgical risk, the sample size shall include a minimum number of 150 patients receiving the subject device for each indicated valve location, each of whom is intended to be studied for at least 1 year (understanding that death occurring prior to 1 year is captured and included in the 1-year follow-up analysis). In addition, at least 400-patient years of data are required in the pre-market setting to assess late adverse events (e.g. thromboembolism, device thrombosis, haemorrhage, infective endocarditis). The 400 patient-years criterion can be met by further pre-market follow-up of the 150 patients beyond 1-year or by enrolment of additional patients. This aligns with sample size requirements for surgical valve replacement devices (see ISO 5840-2:2015). … Table 5 [Table 3 5840-3] below provides a range of sample sizes that will exclude an adverse event rate that is double the expected rate." "Table 5 [Table 3] shows		5910 7.4.6 5840-3 7.4.6

Topic	Definition or Recommendation	Technology	References
	expected AE rates between 1,0 and 10% per year, and an AE rate to exclude from 2,0 to 20% and patient-years necessary between 972 and 97. "The recommendation to collect 400-patient years of data is based upon the following considerations: Using a null hypothesis that the actual adverse event rate is twice the event rate currently accepted for similar devices (See Reference [20]), with probabilities of one-sided type one error of 5 % and probability of type 2 error 20 % (power = 80 %), the sample size (in patient-years) is determined to be 9,72/CR, where CR is the complication rate currently considered acceptable for similar devices. For example, to detect a CR of 2,4 %/year or higher, this would require 9,72/0,024 = 400 patient-years (See Reference [21])." (5910: Gersh 1986, Grunkemeier 1994; 5840-3 see reference Butchart 2018, Grunkemeier 1994) * ISO 5910 ** ISO 5840-3		
OPC/Sample size	" The sample size should be sufficient to enable assessment of the clinical performance of the surgical heart valve substitutes as well as to quantify the associated risk. A minimum of 150 patients in each valve position is required, each of whom is intended to be studied for at least one year (understanding that death occurring prior to one year is captured and included in the one-year follow-up analysis). When appropriate to the study aims, standard statistical methods should be used to calculate the minimum sample size with prior specification of the Type 1 error rate, the statistical power, and effect sizes to be detected (refer to Annex I)." "For a single position valve, a sample size of 800 patient-years is required. If the investigational design is for use in both the aortic and mitral positions, the data shall be presented stratified. A minimum of 400 patient-years are required for each valve position; however, if possible, it is recommended that more than 400 patient-years are collected in both positions to enable more reliable comparisons to the OPC.		5840-2 7.4.6.2 Annex I2

Topic	Definition or Recommendation	Technology	References
	Assuming a one-sided type one error rate of 5 %, with 800 patient-years, only thromboembolism (all positions, both bioprosthetic and mechanical) and major haemorrhage (mechanical valves only) are likely to have at least 80 % power to satisfy the OPC described in the previous paragraph."		
OPC/Sample size, small populations	When using devices in niche indications, rare diseases, or less common patient populations (e.g. paediatric, adult congenital), smaller sample size and shorter premarket follow-up durations may apply but shall be defined and justified based on disease prevalence, unmet clinical needs and risk/benefit considerations. However, this justification does not apply to any post-market clinical follow-up activities for these devices.		5840-2 7.4.6.2
Sample size, small populations	"If the population to be studied is not of acceptable risk to allow surgery to be undertaken, a smaller sample size may be justified based on a robust statistical analysis which takes into consideration the anticipated risk benefit profile. The approved indication for use shall be consistent with evidence gained from the patients studied. Departures from the recommended 400-patient year sample size shall be adequately justified."		5910 7.4.6
	"A statistical justification for the number of patients studied shall be provided based upon the primary hypotheses. No investigational site should enroll more than 50 percent of the total number of study subjects."		7198 10.1.3
	"A statistical justification for the number of patients studied shall also be provided, based upon the clinical hypotheses. The calculation of the number of patients to be enrolled shall take into account patients who will be lost to follow-up."		12417-1 7.3.3

Topic	Definition or Recommendation	Technology	References
	"A justification for the number of investigation sites shall be provided. A justification for the number of patients studied shall also be provided. The calculation of the number of patients to be enrolled shall take into account patients who will be lost to follow-up."		17137 5.7.3
	"A statistical justification for the number of patients studied shall be provided based upon the primary hypotheses. No investigational site should enrol more that 35 % of the total number of study subjects."		25539-1 8.7.3 25539-2 8.7.3
Analysis population	"Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that take into account all the data."		14155 Annex A.7a)
ITT recommended	"The clinical investigation report shall include information on all subjects for whom implantation was planned (i.e. the "intent-to-treat" population). "For randomised studies, the groups shall include all randomised subjects, even those who did not receive the implant. Additional analyses shall be performed on the subjects who actually received the implant.*(refer to Annex J, ISO 5840-1:2021, Annex G, and ISO 5840-1:2021, Annex L). **(see also Annex H and ISO 5840-1:2021, Annex L)***(see also Annexes Q, R,S) The Annexes J (normative) and L provide safety and effectiveness endpoints, Annex G a protocol for echocardiography. The Annexes Q and S show safety and effectiveness endpoints, Annex R shows an imaging protocol. Annex H provides examples for multimodality imaging. "Justification shall be provided for those who were randomized to but did not receive an implant."		ISO 5840-2 7.4.9.5. ISO 5840-3 7.4.9.5 ISO 5910 7.4.9

Topic	Definition or Recommendation	Technology	References
	*ISO 5840-2 **ISO 5840-3 ***ISO 5910		
Unclear whether ITT or PP	"All patients enrolled in the study, including those excluded from the primary endpoint analyses, shall be recorded and reported. The final report shall include current follow-up data on all patients when the required number of patients to test the hypotheses have reached the specified study duration."		ISO 7198 10.1.3
	"All patients enrolled in the study, including those excluded from the primary endpoint analyses, shall be recorded and reported. The final report may be completed when the required number of patients to test the hypotheses has reached the specified study duration. The report shall include current follow-up data on all patients."		25539-1 8.7.3 25539-2 8.7.3
Not more than PP possible	"All patients treated with either test or control VDDCPs, including those excluded from the final analysis, shall be recorded and reported. The final report shall include all follow-up data as specified by the investigation plan."		ISO 12417-1 7.3.3
	"All patients treated with either test or control devices, including those excluded from the final analysis, shall be recorded. The final report shall include all follow-up data as specified by the investigation plan."		ISO 17137 5.7.3
Descriptive statistics	"Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints."		14155 Annex A.7b)
Analysis/ handling of missing data	"Management, justification, and documentation of missing, unused or spurious data, including drop-outs."		14155 Annex A.7 m, n)

Topic	Definition or Recommendation	Technology	References
	"Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable."		
Analysis of statistical uncertainty (random error)	"Analytical procedures including measures of precision such as confidence intervals, if applicable" "The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable. If a hypothesis is tested, a significance level alpha 0.05 (two-sided) and 0.025 (one-sided) and powers between 0,8 and 1 minus alpha need no justification. Depending on the characteristics of the investigational medical device or the clinical investigation, higher or lower levels of significance can be used. Examples of justifications include but are not limited to: product standards, scientific reasons or discussion with regulatory authorities."		14155 Annex A.7c, d)
	"The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable."		14155 Annex A.7h)
	"Description of procedures for multiplicity control and adjustment of error probabilities, if applicable."		14155 Annex A.7k
Handling/ analysis of systematic error (bias)	"Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof." "Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization)."		i, j)

Topic	Definition or Recommendation	Technology	References
	"For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites."		P
Data synthesis methods	"A strategy for pooling data, if applicable."		q
Learning curve	"The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable."		f
Statistical methods for follow-up outcomes	"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 method (see ISO 5840-2:2021, Annex J or ISO 5840-3:2021, Annex H)."		5840-1 Annex L.5
Statistical methods/ OPC	"The use of objective performance criteria (OPC) is the recommended method for the statistical evaluation of adverse event data for new devices based on established device designs." "If objective performance criteria (OPC)-based clinical study design is employed, methods of evaluating clinical data shall include comparing all late complications to the OPC." "Frequentist or Bayesian statistical methods may be used. The manufacturer is responsible for proposing and justifying the specific methodology used." "The formal statistical method applied to OPC specifies that the observed rates should be numerically less than twice the OPC."		5840-2 7.4.6.2 Annex I1, I2
Sub-group analyses	"The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups."		14155 Annex A.7l)

Topic	Definition or Recommendation	Technology	References
	No further considerations on this issue in other ISO, except that in ISO 12417-1: "NOTE In addition, data from a subgroup of patients might be necessary to characterize drug levels in blood over time, if pre-clinical in vivo data indicate drug release occurs over time (this assessment could be conducted as a separate study)." But this does not relate to analysis of different subgroups.		all other included ISO
Analysis of contextual factors			
User proficiency /learning curve	-		
User proficiency /learning curve Statistical methods	"The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable."		ISO 14155 A.7f
Reporting			
RM / benefit-risk analysis reporting	A summary of the benefit-risk analysis shall be disclosed in the relevant clinical investigation documents. The residual risk, including the characterization of their nature (hazards), incidence (occurrence), severity and outcome (harms) shall be disclosed in the IB […] and the	All MD (except IVD)	ISO 14155 6.2.2

Topic	Definition or Recommendation	Technology	References
	instructions for use. The level of detail necessary shall be determined by the sponsor and managed in the interest of subject safety." "The CIP shall include all anticipated adverse device effects and a rationale for the related benefit-risk ratio." "All anticipated adverse device effects shall be disclosed in the informed consent form."		
Content of CIP	A.1.1 "The content of a CIP and any subsequent amendments shall include all the topics listed in this annex." A.1.2 Identification of the CIP, A 1.3 sponsor, A. 1.4 principal investigators, coinvestigators and investigation sites, and A1.5 "Overall synopsis of the clinical investigation: A summary or overview of the clinical investigation shall include all the relevant information regarding the clinical investigation design such as inclusion/exclusion criteria, number of subjects, duration of the clinical investigation, follow-up, objective(s) and endpoint(s). A2 Identification and description of the investigational device, A.3 Justification for the design of the clinical investigation, A4 Benefits and risks of the investigational device, clinical procedure, and clinical investigation, A5 Objectives and hypotheses of the clinical investigation, A6 Design of the clinical investigation, A.6.1 General, A.6.2 Investigational device(s) and comparator(s), A.6.3 Subjects, A.6.4. Procedures, A 6.5 Monitoring plan, A.7 Statistical design and analysis A.8 Data management A.9 Amendments to the CIP, A10 Deviations from clinical investigation plan. A.11 Device accountability A.12 Statement of compliance, A.13 Informed consent process, A.14 Adverse events, adverse device effects, and device deficiencies A.15 Vulnerable population (if applicable), A.16 Suspension or premature termination of the clinical investigation, A. 17 Publication policy, A.18 Bibliography	All MD (except IVD)	ISO 14155 Annex A (normative)
Content of IB	"The content of the IB shall contain, as a minimum, all topics listed in this annex [Annex B]." B.1.2 Identification of the IB, B. 1.3 sponsor / manufacturer, B2 Investigational device	All MD (except IVD)	ISO 14155

Topic	Definition or Recommendation	Technology	References
	information, B.3 Preclinical testing, B.4 Existing clinical data, B.5 Risk management of the investigational device, B.6 Regulatory and other references		Annex B 1 B 2 (normative)
Content of clinical investigation report (CIR)	D.1 General This annex specifies the contents of the clinical investigation report that describes the design, conduct, statistical analysis, and results of a clinical investigation. The format given in this annex may also be used in interim, progress or annual reports, if such reports are required, however some sections might only apply to the final report. D.2 Cover page, D.3 Table of contents D.4 Summary D.5 Introduction, D.6 Investigational device and methods: D.6.1 Investigational device description, D.6.2 Clinical investigation plan (CIP) D.7 Results, D.8 Discussion and overall conclusions, D.9 Abbreviated terms and definitions, D.10 Ethics, D.11 Investigators and administrative structure of clinical investigation, D.12 Signature page, D.13 Annexes to the report	All MD (except IVD)	ISO 14155 Annex D (normative)
Content CI analysis and reporting	The Clinical Investigation Report shall comply with ISO 14155. The Clinical Investigation Report shall include information on all subjects for whom implantation was planned (the “intent-to-treat” population). For randomized studies, the groups shall include all randomized subjects, even those who did not receive the implant. Additional analyses shall be performed on the subjects who actually received the implant (see also Annexes Q, R and S). / Alternative in ISO 5840-2: (refer to Annex J, ISO 5840-1:2021, Annex G, and ISO 5840-1:2021, Annex L)./ Alternative in ISO 5840-3: (see also Annex H and ISO 5840-1:2021, Annex L). Justification shall be provided for those who were randomized to but did not receive an implant.		ISO 5919 7.4.9 ISO 5840-2 7.4.9.5 ISO 5840-3 7.4.9.5

Topic	Definition or Recommendation	Technology	References
	Clinical investigations shall be registered on applicable clinical trial websites upon initiation, with subsequent outcomes reported, including disclosure of both positive and negative results. For both pre- and post-market studies, the following principles shall be followed: a) reports shall state the percentage of follow-up completeness, the reasons for patients lost to follow-up, and provide the total number of patient follow-up years to permit linearized rate calculations for adverse events; b) if investigations have been conducted during follow-up (e.g. echocardiography), the percentage of patients receiving the investigation and how they were selected shall be stated; c) efforts shall be made to ascertain the cause of death, including contact with local physicians if the patient died elsewhere, obtaining details of any investigations performed shortly before death, and autopsy data and explant data if available. Reliance on national healthcare databases to simply record that death has occurred is insufficient. A high percentage of patients with unknown cause of death raises suspicion of device-related deaths.		
	General reference to ISO 14155 and ISO 5840-2 and 5840-3		5840-1 7.4
Content final report	The final report shall include, at a minimum, the following: a) study protocol; b) definitions of reportable clinical events (see Annex A for definitions of potential clinical events); c) justification for selection of the following: 1) study size;		ISO 12417-1 7.3.5

Topic	Definition or Recommendation	Technology	References
	2) choice of control; 3) measurement methods; 4) statistical analyses employed; 5) patient follow-up intervals; d) procedural data and peri-procedural (less than or equal to 30 days after the procedure) and late (more than 30 days after the procedure) follow-up data: 1) patient accountability, including the justification for the exclusion of data; 2) significant and/or relevant deviations from the protocol; 3) summary of patients not completing the study (e.g. lost to follow-up or due to death); 4) summary of reportable clinical events: i) by type of event, including timing of event relative to procedure (i.e. procedural, peri-procedural and for each follow-up time interval); ii) by patient, including timing of events; 5) summary of VDDCP performance; 6) summary of VDDCP performance over time (e.g. VDDCP migration, patency, percentage of diameter stenosis, DCP integrity, unanticipated alterations in shape), if applicable; 7) if required by the protocol, summary of drug levels in the blood over time; 8) summary of target site characteristics related to DCP performance over time;		

Topic	Definition or Recommendation	Technology	References
	9) summary of any intraprocedural, adjunctive or subsequent secondary interventions (e.g. atherectomy, post-dilation) needed after the VDDCP intervention to optimize the results; 10) summary of conversions to non-endovascular operative surgery; 11) summary of peri-procedural and late deaths; 12) summary of pathology, if appropriate, including representative gross photographs and micrographs; 13) comparison of results for test and control groups; 14) conclusions for each specific aim of the study.		
	In addition to the final clinical investigation reporting of specifications outlined in ISO 14155 and ISO 12417-1, a rationale shall be provided for the selection of patient follow-up intervals and for the selection of assessments at each time point based on the degradation profile of the implant		ISO 17137 5.7.5
	The final clinical report shall include the following: a) study protocol, including the following at a minimum: 1) study description (e.g. study design designation, control arm, number of sites, number of patients); 2) primary and secondary endpoints, hypotheses and definitions of success; 3) definition of study success; / ISO 25539-2: in addition, 3) source of data (e.g. site, core lab)) 4) subject population (i.e. selection criteria);		ISO 7198 10.1.5 / ISO 25539-1 8.7.5 ISO 25539-2 8.7.5

Topic	Definition or Recommendation	Technology	References
	5) follow-up intervals; 6) methods of assessment (e.g. clinical, CTA, MRA, duplex ultrasound); 7) data analysis plan; / ISO 25539-2, in addition: including methods to address missing data 8) definitions of adverse events;/ ISO 25539-1 and -2 in addition, definitions of technical and procedural success, device and clinical effects of failure and adverse events; b) rationale, based on the risk assessment and questions to be answered, for selection of the following: 1) study size; 2) choice of control; 3) measurement methods; 4) statistical analyses employed; 5) patient follow-up intervals; c) number of patients treated at each investigational site; d) follow-up accountability (e.g. numbers of patients eligible for each follow-up interval and the number with specified follow-up data), including a rationale for the exclusion of data from the primary endpoint analyses; e) demographics and risk factors;/ ISO 25539-1 -2: demographics, risk factors and relevant vascular lesion characteristics (e.g. sizes of aneurysm treated (25539-1 only), lengths of the stenotic lesions);		

Topic	Definition or Recommendation	Technology	References
	f) diameters of devices used; / ISO 25539-1 and -2: numbers of devices per patient and sizes of devices used; g) significant and/or relevant deviations from the protocol; in ISO 25539-2 in addition, and the manner in which deviations were addressed in the data presentation; h) results: 1) primary and secondary outcomes: i) safety; ii) effectiveness; 2) comparison of results for test and control groups; i) conclusions from study, including results of hypothesis testing and achievement of success as defined by the protocol. h Alternative in ISO 25539-1 and -2: h) results: 1) technical success; 2) procedural success; 3) safety: i) primary and secondary endpoint outcomes;		

Topic	Definition or Recommendation	Technology	References
	ii) summary of peri-procedural (less than or equal to 30 days, or prior to hospital discharge) and late conversions to open surgery; iii) summary of peri-procedural and late deaths; 4) effectiveness: i) primary and secondary endpoint outcomes; ii) summary of secondary interventions; 5) summary of explant analyses; / not in ISO 25539-2 6) conclusions from study, including results of hypothesis testing and achievement of success as defined by the protocol.		
Justification of trial design / CIP	A.3 Justification for the design of the clinical investigation, which shall be based on the conclusions of the clinical evaluation, as specified in 6.3, and shall comprise a) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable carried out to justify the use of the investigational device in human subjects, b) an evaluation of clinical data that are relevant to the proposed clinical investigation, c) a description of the clinical development stage (see Annex I), if appropriate	All MD (except IVD)	ISO 14155 Annex A 3; (normative)
Justification of trial design / IB	"B.2a Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device. […] B.2h Description of the intended clinical performance."	All MD (except IVD)	ISO 14155

Topic	Definition or Recommendation	Technology	References
	"B.3 Preclinical testing. Summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing, justifying its use in human subjects. The summary shall include or, where applicable, refer to the results of a) design calculations, b) in vitro tests, c) mechanical and electrical safety tests, d) reliability tests, e) validation of software relating to the function of the device, f) any performance tests, g) ex vivo tests, h) in vivo animal test, i) evaluation of biological safety, j) validation of procedures for cleaning, disinfection, or sterilization." "B.4 Existing clinical data. a) Summary of relevant previous clinical experience with the investigational device and with medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device. b) Analysis of adverse device effects and any history of modification or recall." "B.5 Risk management of the investigational device. a) Summary of the benefit-risk analysis including identification of residual risks. b) Contra-indications and warnings for the investigational device." "B.6 Regulatory and other references. a) List of international standards, if any, complied with in full or in part. b) Statement of conformity with national regulations, where appropriate. c) List of references, if relevant.		Annex B 3; B 4; B 5 (normative)
Justification of trial design / CIR	"The introduction shall contain a brief statement placing the clinical investigation in the context of the development of the investigational device and relating the critical features of the clinical investigation (e.g. objectives and hypotheses, target population, treatment and	All MD (except IVD)	ISO 14155 Annex D.5 (normative)

Topic	Definition or Recommendation	Technology	References
	follow-up duration) to that development. Any guidelines that were followed in the development of the CIP or any other agreements/meetings. between the sponsor and regulatory authorities that are relevant to the particular clinical investigation should be identified or described.		
Objectives / Research question / CIP	A.4 Benefits and risks of the investigational device, clinical procedure, and clinical investigation a) Anticipated clinical benefits. b) Anticipated adverse device effects (see 6.2.2). c) Risks associated with participation in the clinical investigation (see 6.2.3). d) Possible interactions with concomitant medical treatments as considered under the risk analysis. e) Steps that will be taken to control or mitigate the risks. f) Rationale for benefit-risk ratio. A.5 Objectives and hypotheses of the clinical investigation a) The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified. b) Objectives, primary and secondary, described as 'superiority', 'non-inferiority', or 'equivalence', if applicable.	All MD (except IVD)	ISO 14155 Annex A 4; A.5 (normative)

Topic	Definition or Recommendation	Technology	References
	c) Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable. d) Primary and secondary hypotheses, if applicable. e) Risks and anticipated adverse device effects that are to be assessed. The objective(s) shall serve the purpose of the clinical investigation and shall relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population. The objectives of the clinical investigation shall translate directly into the pre-specification and operationalisation of the primary endpoint(s). Claims shall be linked to eligibility criteria for subject and users.		
Objectives / Research question / IB	B.2a Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device.	All MD (except IVD)	ISO 14155 Annex B (normative)
Objectives / Research question / CIR	See Summary of CIP		Annex D.6.2
Design type and general design issues/ description/ justification CIP	A.6.1 General a) Description of the design type of clinical investigation to be performed (e.g. randomized, blinded or open-label, parallel groups or crossover, multicentre, international) the control group, (e.g. comparative claim and reversible treatment of a chronic state) and the comparator with rationale and justification for the choice. Absence of control(s) shall be justified.		ISO 14155 Annex A.6.1

Topic	Definition or Recommendation	Technology	References
	b) Description of the measures to be taken to minimize or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors. c) Primary and secondary endpoints, with rationale for their selection and measurement. If applicable, composite endpoints, with rationale for their selection and measurement. The primary endpoint shall be appropriate for the investigational device and should be clinically relevant. NOTE Composite endpoint is a pre-specified combination of more than one endpoint and can be used cautiously by including only components that have relatively equal clinical importance, frequency, and anticipated response to the presumed mechanism of action. d) Methods and timing for assessing, recording, and analysing variables. e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration. f) Any procedures for the replacement of subjects (generally, not applicable to randomized clinical investigations). g) Investigation sites: number, location, and, if appropriate, differences in investigation site environment. h) Definition of completion of the clinical investigation (see 8.1).		
Population /CIP	A.6.3 Subjects a) Inclusion criteria for subject selection.		ISO 14155 Annex A.6.3

Topic	Definition or Recommendation	Technology	References
	b) Exclusion criteria for subject selection. c) Criteria and procedures for subject withdrawal or lost to follow-up 1) when and how to withdraw a subject from the clinical investigation or stop the use of the investigational device, 2) documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons, 3) whether and how subjects are to be replaced. d) Point of enrolment. e) Point of randomization, if applicable. f) Total expected duration of the clinical investigation. g) Expected duration of each subject's participation. h) Number of subjects required to be included in the clinical investigation, and where needed, anticipated distribution of enrolment among the participating investigation sites. i) Estimated time needed to select this number (i.e. enrolment period). j) Relationship of investigation population to target population. k) Information on vulnerable, pregnant, and breastfeeding population, if applicable		
Intervention description / CIP	A.6.2 Investigational device(s) and comparator(s) a) Description of the exposure to the investigational device(s) or comparator(s), if used.		ISO 14155 Annex A.6.2

Topic	Definition or Recommendation	Technology	References
	b) List of any other medical device or medication to be used during the clinical investigation if not already specified in the instructions for use. c) Number of investigational devices to be used, together with a justification.		
Comparator / CIP	See above		ISO 14155 Annex A.6.2
Intervention description / IB	B.2 “b) Statement concerning the regulatory classification of the investigational device, if relevant. c) General description of the investigational device and its components, […]” B.2 “e) Description of the mechanism of action of the investigational device, along with supporting scientific literature. f) Manufacturer's instructions for installation, maintenance of hygienic conditions and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use […] g) Sample of the label, for example sticker or copy, and instructions for use or reference to, and information on any training required.	All MD (except IVD)	ISO 14155 Annex B.2 (normative)
Outcome / CIP			ISO 14155 Annex A.6.2
Summary of CIP in the CIR	A summary of the CIP, including any subsequent amendment(s) with a rationale for each amendment, shall be provided. The summary shall include a brief description of the following: a) the clinical investigation objectives; b) the clinical investigation design including	All MD (except IVD)	ISO 14155 Annex D.6.2

Topic	Definition or Recommendation	Technology	References
	1) the type of clinical investigation, 2) the clinical investigation endpoints, and 3) the control group; c) the ethical considerations; d) the data quality assurance; e) the subject population for the clinical investigation, with the 1) inclusion/exclusion criteria, and 2) sample size; f) the treatment and treatment allocation schedule; g) any concomitant medications/treatments; h) the duration of follow-up; i) the statistical design, analysis, and justifications including 1) the clinical investigation hypothesis or pass/fail criteria, 2) a sample size calculation, 3) statistical analysis methods, 4) interim analyses, if applicable.		
Intervention description/CIP			

Topic	Definition or Recommendation	Technology	References
Intervention description/ IB			
Intervention description/ CIR	D.6.1 Investigational device description The description of the investigational device shall contain the following: a) a description of the investigational device; b) the intended use of the investigational device(s); c) previous intended uses or indications for use, if relevant; d) any changes to the investigational device during the clinical investigation or any changes from the IB, including 1) raw materials, 2) software, 3) components, 4) shelf-life, 5) storage conditions, 6) instructions for use, and 7) other changes.	All MD (except IVD)	ISO 14155 Annex D.6.1
Statistical methods/ CIP	With reference to A.5 and A.6, the description of and justification for statistical design and analysis of the clinical investigation shall cover the following:		ISO 14155 Annex A.7

Topic	Definition or Recommendation	Technology	References
	a) Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that take into account all the data. b) Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints. c) Analytical procedures including measures of precision such as confidence intervals, if applicable. d) The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable. If a hypothesis is tested, a significance level alpha 0,05 (two-sided) and 0,025 (one-sided) and powers between 0,8 and 1 minus alpha need no justification. Depending on the characteristics of the investigational medical device or the clinical investigation, higher or lower levels of significance can be used. Examples of justifications include but are not limited to: product standards, scientific reasons or discussion with regulatory authorities. e) Sample size calculation and justification taking into account: 1) all relevant clinical data on outcome variable and effect size, if applicable; 2) assumptions of expected outcomes across treatment groups, if applicable; 3) adjustments due to any pre-planned interim analyses, if applicable; 4) detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable; 5) randomization allocation ratio (e.g. 1:1, 1:2), if applicable;		

Topic	Definition or Recommendation	Technology	References
	6) expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint). All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided. For exploratory and observational clinical investigations (see Annex I), in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size shall be provided. f) The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable. g) Pass/fail criteria to be applied to the results of the clinical investigation. h) The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable. i) Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof. j) Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization). k) Description of procedures for multiplicity control and adjustment of error probabilities, if applicable. l) The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.		

Topic	Definition or Recommendation	Technology	References
	m) Management, justification, and documentation of missing, unused or spurious data, including drop-outs. n) Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable. o) Procedures for reporting any deviation(s) from the original statistical analysis plan. p) For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites. q) A strategy for pooling data, if applicable. Further or more specific information can be found in standards for different types of medical devices or in national regulations or guidance documents (see References [9], [10], [13]).		
User dependency/ learning curve	-		
Description of results / CIR	The results section shall include the following: a) the clinical investigation initiation date; b) the clinical investigation completion/suspension date; c) the disposition of subjects; numbers screened, randomized and received therapy; d) the disposition of investigational devices;	All MD (except IVD)	ISO 14155 Annex D.7

Topic	Definition or Recommendation	Technology	References
	e) the subject demographics and other relevant baseline characteristics; f) CIP compliance; g) an analysis with rationale and justifications, which includes 1) all clinical performance, effectiveness or safety analyses provided for in the CIP, NOTE These include results for the components of composite endpoints, when used. 2) a summary of all adverse events and adverse device effects, including a discussion of the severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure, 3) a table compiling all observed device deficiencies that could have led to a serious adverse device effect, and any corrective actions taken during the clinical investigation, if any, 4) any needed subgroup analyses for special populations (i.e. gender, racial/cultural/ethnic subgroups), as appropriate, 5) an accountability of all subjects with a description of how missing data or deviation(s) were dealt with in the analysis, including subjects i) not passing screening tests, ii) lost to follow-up, and iii) withdrawn or discontinued from the clinical investigation and the reason. 6) clear distinctions between primary analyses, other pre-specified analyses, and additional analyses,		

Topic	Definition or Recommendation	Technology	References
	h) listings of deaths and reasons for deaths		
Elements of discussion / CIR	D.8 Discussion and overall conclusions The conclusions shall be based on the intended use and target population of the investigational device and shall include the following: a) the clinical performance, effectiveness, or safety results and any other endpoints; b) an assessment of benefits and risks; c) a discussion of the clinical relevance and importance of the results in the light of other existing data; d) any specific benefits or special precautions required for individual subjects or groups considered to be at risk; e) any implications for the conduct of future clinical investigations; f) any limitations of the clinical investigation including but not limited to: 1) selection, retention, and compliance of subjects, 2) selection, retention, adherence (to CIP, instructions for use and the requirements of this document) of investigation sites and users, and investigation site environment type(s), 3) bias introduced by missing observations, by confounders and by 1) and 2) above. Requirements in f) also apply to the control group(s).	All MD (except IVD)	ISO 14155 Annex D.8
Ethics / CIR	The ethics section shall include the following:	All MD (except IVD)	ISO 14155 Annex D.10

Topic	Definition or Recommendation	Technology	References
	a) confirmation that the CIP and any amendments to it were reviewed by the EC (if required); b) b) list of all ECs consulted (can be given in an annex; see D.13); c) c) confirmation that the clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki; d) d) statement that informed consent was obtained and when it was obtained.		
Administrative structure of CI /CIR	D.11 Investigators and administrative structure of clinical investigation The overview of the administrative structure shall include the following: a) a brief description of the organization of the clinical investigation; b) a list of investigators, including their affiliations (can be given in an annex; see D.13); c) the names and addresses of any external organizations (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation (can be given in an annex; see D.13); d) the names and addresses of the sponsor(s) or sponsors' representative(s).	All MD (except IVD)	ISO 14155 Annex D.11
Annexes /CIR	There can be annexes to the report which contain the following: a) the CIP, including amendments; b) the instructions for use; c) the list of principal investigators and their affiliated investigation sites, including a summary of their qualifications or a copy of their CVs; d) the list of names and addresses of any external organizations (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation;	All MD (except IVD)	ISO 14155 Annex D.13

Topic	Definition or Recommendation	Technology	References
	e) the list of monitors; f) the list of ECs; g) the tabulation of all relevant data sets, including 1) CIP deviations that can have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, 2) all adverse events, adverse device effects and device deficiencies, and 3) withdrawals and discontinuations, h) the audit certificate, if applicable.		
Reducing wasted research and publication bias			
Study registries			
Registration	"In accordance with the Declaration of Helsinki, a description of the clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation."		ISO 14155 5.4 8.4 A.17

Topic	Definition or Recommendation	Technology	References
	"The results of the clinical investigation shall be entered in a publicly accessible database where the clinical investigation was registered (see 5.4) and published whether positive, inconclusive or negative, to help guide future research, device development and medical treatment." CIP: "Statement that the clinical investigation will be registered in a publicly accessible database (see 5.4)."		
Registration	"Clinical investigations shall be registered on applicable clinical trial websites upon initiation where possible."		ISO 5840-2 7.4.9.5
	"Clinical investigations shall be registered on applicable clinical trial websites upon initiation,"		ISO 5840-3 7.4.9.5 ISO 5910 7.4.9
Reporting	"Subsequent outcomes shall be reported, including disclosure of both positive and negative results, in accordance with applicable requirements. For both pre- and post-market studies, the following principles shall be followed: a) reports shall state the percentage of follow-up completeness, the reasons for patients lost to follow-up, and shall provide the total number of patient follow-up years to permit linearized rate calculations for adverse events; b) if investigations have been conducted during follow-up (e.g. echo), the percentage of patients receiving the investigation shall be stated and how they were selected;		ISO 5840-2 7.4.9.5

Topic	Definition or Recommendation	Technology	References
	c) efforts shall be made to ascertain the mode of death and the cause of death, including contact with local physicians if the patient died elsewhere, obtaining details of any investigations performed shortly before death, and post-mortem examination data and explant data if available; reliance on national healthcare databases to simply record that death has occurred is insufficient; a high percentage of unknown cause of death may raise suspicion of device-related deaths."		
	"… with subsequent outcomes reported, including disclosure of both positive and negative results. For both pre- and post-market studies, the following principles shall be followed: a) reports shall state the percentage of follow-up completeness, the reasons for patients lost to follow-up, and provide the total number of patient follow-up years to permit linearized rate calculations for adverse events; b) if investigations have been conducted during follow-up (e.g. echo), the percentage of patients receiving the investigation shall be stated and how they were selected; c) efforts shall be made to ascertain the cause of death, including contact with local physicians if the patient died elsewhere, obtaining details of any investigations performed shortly before death, and post-mortem examination data and explant data if available; reliance on national healthcare databases to simply record that death has occurred is insufficient; a high percentage of unknown cause of death may raise suspicion of device-related deaths."		ISO 5840-3 7.4.9.5 ISO 5910 7.4.9

CORE-MD

CORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

For more information, visit: www.core-md.eu

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