Recommendations on study design of pivotal clinical investigations for high-risk medical devices by regulators and ISO

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Who benefits from study design recommendations?

- **Manufacturers**
- **Clinical investigators** undertaking trials
- **Expert panels** advising manufacturers of class IIb and III devices regarding clinical development strategy and clinical investigations [MDR Article 61.2]
- **Competent authorities** approving design of clinical investigations [Article 71]
- **Expert panels** reviewing Clinical Evaluation Assessment Reports
- **Notified Bodies** evaluating the quality and validity of clinical investigations
- **EU Regulators** preparing guidance or common specifications

Objectives of the systematic review [CORE-MD Task 1.4]

1) To identify and describe recommendations on methodology of design of **confirmatory pivotal clinical trials** for **high-risk medical devices** from:
   1) Regulators, national and transnational of high-income countries: **EU, EFTA, UK,USA, Canada, AUS, Japan**
   2) International Standardization Organization
   3) Public-private consortia of regulators, academia and clinical experts
2) Compare and describe similarities and differences
3) Identify gaps for research on trial methodology

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 investigations	First in human clinical investigation Early feasibility clinical investigation Traditional feasibility clinical investigation	Pivotal clinical investigation	Post-market clinical investigation	Registry[a] Post-market clinical investigation[a]
Burden to subject	Interventional			Non-interventional

[a] 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.

Type of documents included: general guidance docs for medical devices with recommendations including confirmatory trials, and device-specific guidance in the cardiovascular, orthopaedic, diabetic field published > 2000; Devices: High-risk class IIb and III

Find review protocol at: ***https://osf.io/3mf7v***

Data extracted for 7 topics

Definitions of **level of evidence**, descriptions of **study types**

Need for **clinical investigations**, criteria for **substantial equivalence**

Advice on **appropriate choice** of study design and methodology

Recommendations on general aspects of design: **study objectives, PICO, and validity**

Recommendations on **statistical methods**

Any consideration of **context of use** and **learning curve**

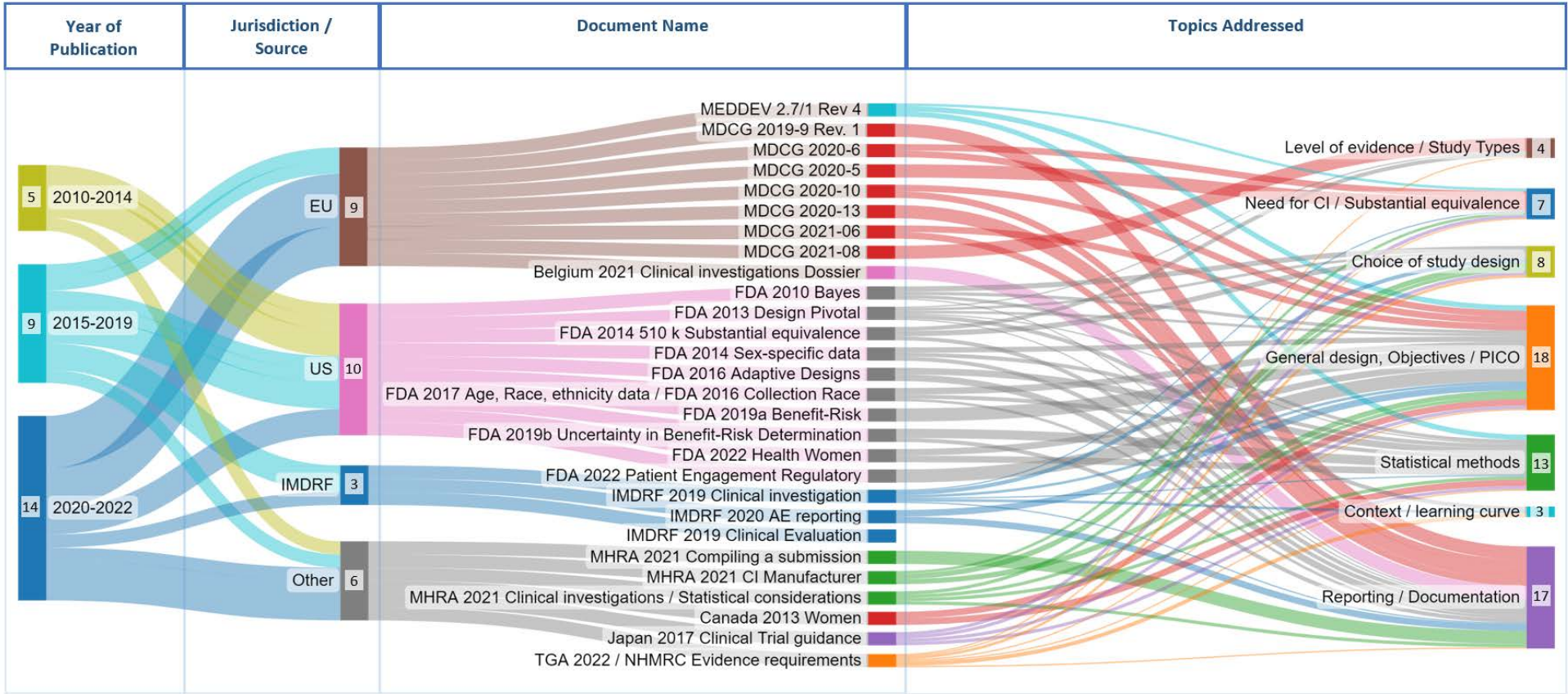
Requirements for reporting clinical evidence

Results: Included documents after full text screening with recommendations on trial design aspects

Document type	#	Details
ISO	12	3 general, 8 on cardiovascular implants
National Regulators	19	11 FDA/ 1 Ca / 3 UK / 1 BE / 2 AUS / 1 JAP
EU	8	7 MDCG / 1 MEDDEV
IMDRF	3	
Overall	42	

Recommendations from regulatory guidance documents

Overview of topics addressed



EU regulatory documents	Level of evidence/ Study Types	Need for CI/ Substantial equivalence	Choice of study design	General design, Objectives / PICO	Statistical Methods	Context / learning curve	Reporting
MEDDEV 2.7/1 Rev 4 2016 Clinical Evaluation	-	X	-	X	X	-	
MDCG 2019-9 Rev. 1 SSCP	-	-	-	-	-	-	X (SSCP)
MDCG 2020-6 Clinical evidence legacy devices	-	X/	-	X (O)	-	-	-
MDCG 2020-5 Equivalence	-	/X	-	-	-	-	-
MDCG 2020-10 Safety reporting in clinical investigations	-	-	-	X (O)	-	-	X (safety)
MDCG 2020-13 CEAR template	-	-	-	-	-	-	X
MDCG 2021-06 Q&A CI	-	-	-	X (O)	-	-	X
MDCG 2021-08 CI application / notification	/x	-	-	-	-	-	-
Belgium 2021 Clinical investigations Dossier	-	-	-	-	-	-	CIP, IB, CEP

CEP: clinical evaluation plan, CIP: Clinical investigation plan, IB: investigator's brochure, O: outcome, PICO: Population-Intervention-Comparator-Outcome, SSCP: summary of safety and clinical performance

EU Guidance and National Belgian Guidance

- **MDCG guidance** focuses on 4 of 7 topics:
  Need for clinical investigation / equivalence / reporting /
  general study design: mainly outcome definitions
  Mentions levels of evidence only in context of clinical evaluation (not investigation!) of legacy devices.
- **Belgium:** document provides reporting/ documentation structure for dossier content, complements ISO 14155 templates.
- **MEDDEV 2.7/1 (rev 4)** on clinical evaluation, some parts relevant for CI

Topics: need for clinical investigation / equivalence, general study design /PICO: the latter covered in detail: definition of PICO and validity criteria for studies

FDA guidance documents

FDA regulatory documents	Level of evidence/ Study Types	Need for CI / Substantial equivalence	Choice of study design	General design & objectives / PICO	Statistical Methods	Context / learning curve	Reporting
FDA 2010 Bayes	-	-	X	X	XX	-	X (protocol)
FDA 2013 Design Pivotal	XX	-	X	XX	X	X	X (protocol)
FDA 2014 510 k Substantial equivalence	(X)*	- / X	-	-	-	-	X
FDA 2014 Sex-specific data	-	-	-	X (P)	X	-	X
FDA 2016 Adaptive Designs	-	-	-	-	XX	-	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 Women	-	-	-	X (P)	X	-	-
FDA 2022 Patient Engagement	-	-	-	X (P, O)	-	-	-

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* Provided study type list with descending evidence level in Appendix
FDA: Food and Drug Administration USA, O: outcome, P: population, PICO: Population-Intervention-Comaprator-Outcomes
SSED: summary of safety and effectiveness data

FDA Guidance

- "**Design considerations on pivotal MD trials**" (2013) most comprehensive. Covers guidance on level of evidence, choice of study design, general design issue/ PICO, and statistical methods
- **Newer developments in study design are considered with detailed guidance** Bayesian & adaptive designs might reduce sample sizes and address uncertainty in elements of study design (effect size, variability of effect, etc).
- **Subgroup analyses** for different treatment effects (gender, age, ethnicity) and methods to address under-representation of population subgroups.
- **Patient engagement** in planning of clinical investigation design is addressed

Regulatory Documents of IMDRF and 4 countries	Level of evidence Study Types	Need for CI/ Substantial equivalence	Choice of study design	General design & objectives / PICO	Statistical methods	Context / learning curve	Reporting
IMDRF 2019 Clinical investigation	-	X	X	X	X	X	X
IMDRF 2019 Clinical Evaluation	-	-	-	-	-	-	-
IMDRF 2020 AE reporting	-	-	-	X (O)	-	-	X (safety)
TGA 2022 / NHMRC Evidence requirements	X	X	X general X device-specific	X general X device-specific	X	X	X ISO 14155 and reporting guidelines
MHRA 2021 Compiling a submission	-	-	-	-	-	-	X CIP ISO p8f IB ISO
MHRA 2021 CI Manufact.	-	X	X	X	-	-	-
MHRA 2021 Clinical investigations / Statistical considerations	-	-	X	X	X	-	X
Canada 2013 Women	-	-	-	X	X	-	-
Japan 2017 Clinical Trial guidance	-	X	X	X	X	-	-

CI = clinical investigation, CIP = clinical investigation plan, CEP = clinical evaluation plan,
IB = investigator's brochure, ISO = International Standardization Organization, PICO: Population-Intervention-Comparator-Outcome

Guidance from other jurisdictions

- **IMDRF** on clinical investigations addresses 6 of 7 topics.
  But it lists only factors to consider, without suggesting details how or explanations
  No hierarchy of study designs provided.

- **TGA (Australia):** focuses mainly on clinical evaluation, document covers all topics and gives device-specific recommendations. **Contains hierarchy of evidence**.
  Short section on design of clinical investigations refers to IMDRF and of MEDDEV 2.7/1 Rev. 4.

- **MHRA (UK):** 3 documents cover 5 of 7 topics, guidance very concise, recommendations are for all studies (developmental stages and risk classes).

- **PDMA (Japan):** (4 of 7 topics) focus on need for a clinical investigation and choice of study designs, but details of design only touched rudimentarily.

CORE-MD – gaps identified

- **Methods of developing recommendations**
  Only TGA provides brief description. FDA mentions preparatory workshops. Methods to identify current state of science are particularly important for device-specific guidance
- **Guidance on choice of study design**
  Need to distinguish more systematically between established and novel high-risk medical devices.
- **Objective performance criteria (OPCs)**
  Recommended for established devices but no guidance how OPCs should be derived that they reflect change in standard of care, different populations, and statistical issues

ISO Standards
12 Documents

Results: CEN/ISO Standards with CI recommendation

General	Heart valves	Stents, grafts & patches
14155:2020 Clinical investigations of medical devices – Good clinical practice, Harmonised European Standard for MDD; Standardisation request for MDR	5840-1:2021 Cardiac valve prostheses. General requirements Standardisation request for MDR	7198:2016 Vascular grafts and patches No harmonised EN Standard / No request
14971:2019 Application of risk management to medical devices Harmonised European Standard for MDR	5840-2:2021 Cardiac valve prostheses. Surgically implanted valves Standardisation request for MDR	DIS 12417-1:2021 Vascular device-drug combination products. General requirements Standardisation request for MDR
24971:2020 Guidance on 14971 Not eligible for harmonisation	5840-3:2021 Cardiac valve prostheses. Transcatheter implanted valves Standardisation request for MDR	TS 17137:2021 Cardiovascular absorbable implants Technical specifications are not eligible for harmonisation
	5910:2018 Cardiac valve repair devices No harmonised EN Standard / No request	25539-1:2017 Endovascular prostheses Standardisation request for MDR
		25539-2:2020 Vascular stents Standardisation request for MDR

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

Covers all non-IVD studies of **all risk classes** at **all stages** of clinical development

Recommendations are very general and rarely study type specific

Contains annexes with reporting structures of the study protocol, the study report and the "Investigator's Brochure"

ISO 14155

Description of study types	No hierarchy of study types Design types used: "**exploratory, confirmatory, observational**" Confirmatory study: "**adequately controlled**" intervention study with **pre-specified hypotheses** for the primary endpoint(s) and the **correct confirmatory statistical tests**. (Appendix I 4.3)
Need for a clinical investigation	CI, if residual risk identified in risk analyses is balanced against anticipated benefits. **Risk assessment shall include review of published and unpublished medical and scientific data.** → ISO 14971, 24971
Choice of study design	Clinical evaluation / risk assessment determine **required development stage**(s) and **justify optimal design**, identify relevant endpoints, confounding factors, **justify choice of control group**, use of randomisation, blinding etc. Clinical evaluation **includes assessment** of performance, clinical effectiveness **of similar devices or therapies.**

ISO 14155

Statistical methods	**Annex A for CIP**: Description of 17 items of statistical methods required. **Justification of sample size** and methods, **taking into account all the data** (handling missing values), handling of statistical uncertainty, **significance level for alpha= 0.05**, **power between 0.8 and 1** need no justification. Methods for interim analysis, multiplicity control, **management of systematic errors**, imbalances between study centers

Summary of guidance in ISO standards

- Limited number of ISO standards for implants with requirements on clinical investigations
- Device-specific ISO standards: different degree of detail in recommendations
- Differences in recommendations, e. g. on study type not necessarily due to differences in the nature of the device
- Unclear how the current state of science in the medical field is considered in the device-specific ISO

Results: Recommendations device-specific ISO

Design recommendation	Heart valves ISO 5840-1, -2, -3, 5190	Stents, grafts & patches ISO 7198, 12417-1, 17137, 25539-1,-2
Description of study types	None	7198, 25539-1 use FDA classification only descriptively
When is a clinical investigation needed?	For new devices and expanded indications	
	Device modifications: Justification if no CI	7198, 25539-1,-2: for significant changes CI needed, justification if no CI, no statement by other 2 ISO
Choice of study type	**RCT,** but depending on purpose, **novel vs. modification or well-established** technology ISO 5840-2 recommends **objective performance criterion comparison for established devices** with sample size calculation in annex I	17137: sufficiently powered RCT Other 4 ISO: **Controlled multi-center trials with at least 3 sites**, justification if no control.

Results: Recommendations device-specific ISO

Design recommendation	Heart valves ISO 5840-1, -2, -3, 5910	Stents, grafts & patches ISO 7198, 12417-1, 17137, 25539-1,-2
Population	Include **enough subjects, investigators, institutions to be representative for intended patient/user population** Disease/device-specific inclusion criteria listed, **criteria for institutions** (case-mix, skills, training)	All: inclusion/exclusion criteria should be clearly defined Criteria **should specify target population** and **accessible population**
Comparator	**Active control** with comparable device or another **active comparator** ISO 5840-2 OPC for established devices	1: as heart valve ISO **4 ISO repeat ISO 14155 recommendation** (dependent on clinical evaluation)
Outcomes	Safety and effectiveness endpoints have to be **prospectively specified** Don't use single composite endpoints, additionally components as secondary ep.	Safety and effectiveness endpoints have to be **prospectively specified** S25539-1,-2:specify components of composite endpoint as secondary endpoint
Annexes for endpoints and imaging protocols	Normative: **all endpoints** 5840-1 annex L, **adverse event classification** 5840-2, -3, 5910 annex J, G, Q Informative: all endpoints 5910 annex S, imaging protocols 5840-2, -3 annex H, R	Informative: Description of device effects of failure and clinical effects of failure 25539-1, -2 annex B and B, C

Challenges and gaps identified

- EN ISO 14155: providing general requirements on GCP, not aiming specifically to guide design of pivotal studies on high-risk medical devices → Guidance specific to high-risk devices distinguishing established and new devices could be useful
- Device-specific ISO: Only a limited number with CI recommendations available → Recommend more such ISO requirements or a task for Common Specifications?
- Current state of the art must be reflected in device-specific ISO → Systematic literature reviews needed / special attention to consensus statements from representative groups of professionals.
- Methods for deriving recommendations for clinical investigations were not described. (Common) methodology of CI part for device-specific ISO needed.

Thank you for your attention!

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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.

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For more information, visit: www.core-md.eu

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