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Study Design Recommendations in ISO Standards for High-risk Medical Devices, a Systematic Review of the Horizon2020 CORE-MD Project

Schnell-Inderst P[1], Kühne F[1], Holborow R[2], Rochau U[1], Siebert U[1]

(1)Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health, Health Services Research and Health Technology Assessment, UMIT TIROL- University for Health Sciences and Technology, Hall i.T., Austria
(2)BSI, Milton Keynes, UK

Contact: petra.schnell-inderst@umit-tirol.at

Background:

The role of harmonized European standards (HES) is key in the certification of medical devices (MD) in the European Union. When the product is designed and manufactured according to applicable HES, it can benefit from a presumption of conformity (MDCG 2021-5). HES are considered as reflecting the state-of-the-art in the corresponding medical field.

Objectives:

To perform a systematic review to identify guidance on the design, analysis, and reporting of confirmatory pivotal clinical trials for high-risk MD, from the International Standardization Organization (ISO).

Methods:

We used the list of ISO 16142-1: 2016 providing guidance on relevant ISO standards for non-in vitro diagnostic devices, and searched the online browsing platform of ISO for later published standards on MD. We included general ISO standards on MD as well as device-specific standards on high-risk cardiovascular, orthopedic, and diabetes MD, if they contained substantial recommendations on clinical investigations. Two reviewer screened the identified ISO standards against inclusion and exclusion criteria using the title and description on the ISO website. Standards identified as potentially relevant were checked by one reviewer who had access to ISO full texts, and those included were finally ordered in full text and checked by two reviewers. We extracted recommendations from included ISO standards according to several predefined topics and subtopics on study design, data analysis and reporting.

Table: Recommendations on study design in 9 ISO standards of cardiovascular implant devices

	Heart valves 5840-1,-2, -3, 5910	Other cardiovascular implants 7198, 12417-1, 17137, 25539-1, -2
When is a clinical investigation needed?	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
Study type recommended	RCT depending on purpose, novel vs. modification or well-established technology	17137: sufficiently powered RCT Other 4 ISO: Controlled multi-center trials with at least 3 sites, justification if no control.
	ISO 5840-2 recommends OPC comparison for established devices with sample size calculation in annex I	
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

CI: clinical investigation, ISO: International Standardization Organization standard, RCT: randomized controlled trial

Results:

Out of 689 ISO standards, 17 were checked in full text and 12 ISO standards published between 2016 and 2021 were included: Three relate to MD in general, nine to cardiovascular implants. ISO 14155:2020 on good clinical practice for clinical investigations of MD does not provide a hierarchy of evidence levels by study designs. The study design should be derived from the clinical evaluation and the risk analysis necessary to prepare the study. Recommendations are very general and rarely study type specific. The device-specific standards covered heart valves (n=4) and other implants such as coronary stents and endovascular grafts (n=5). Recommendations when a clinical investigations are needed and on the choice of study design for a pivotal trial are shown in the Table. All heart valve and one other implant standard recommend randomized controlled trials and distinguish between novel and well-established MD. Four standards recommend as a minimum multi-center trials with at least 3 sites and a control group. ISO standards do not report the methods how recommendations were developed. It is unclear, how the current state-of-the-art in the medical field is considered. There is no indication of a literature search.

Conclusion:

Recommendations on the design of pivotal clinical trials for cardiovascular high-risk MD are heterogeneous. Given the importance of ISO standards for the certification of MD, the methods for their development should be explicit, transparent, and based on science.

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