CORE-MD

Coordinating Research and Evidence for Medical Devices

Proposals for a hierarchy of clinical study designs

Deliverable 2.3

Deliverable factsheet

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**Note for the reviewers: the present deliverable contains a set of initial proposals to build a hierarchy of clinical study designs that has been iteratively discussed and refined until the end of the project. The first version was prepared in view of the stakeholder workshop organized in Brussels on the 21st of November 2024 (M32) during which it was discussed with invited clinical study design experts and regulators. For this reason, the final delivery has been postponed until the end of the project.*

Acronyms and abbreviations

EU	European Union
IDEAL-D	Idea, Development, Exploration, Assessment, Long-term study - Devices
MDR	Medical Device Regulation
RCT	Randomized clinical trial
CE	Conformité européenne

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Executive Summary

No detailed requirements for stepwise clinical evaluation of high-risk medical devices are endorsed by European regulations or guidance. The Medical Device Regulation (MDR) requires that a medical device has a positive benefit/risk ratio, but the methodology for clinical studies to establish this has not been elaborated. The deliverable 2.3 is articulated as an overview of the current landscape of clinical investigations that may be employed for the evaluation of the performance and safety of high-risk medical devices. The main messages and conclusions of the deliverable are:

- Study designs are conventionally graded in a hierarchy based on their inherent risk of bias. The concept of the "pyramid of evidence" has become well established in medicine and clinical research.
- Randomized clinical trials (RCTs) are at the top of the pyramid and are considered the cornerstone of modern evidence-based medicine.
- Based on existing models of multi-stage development, a high-risk medical device should be evaluated progressively with study designs appropriate to each stage of development.
- Optimal study designs may be different according to the category of the device being evaluated (e.g., established versus innovative device).

1 Introduction

The MDR imposes more stringent standards for generating and assessing evidence on the performance and safety of high-risk medical devices than was required under the previous medical device directives, and it specifies in particular that "clinical investigations shall be performed for implantable and other high-risk medical devices" [1]. Different study designs may be used in the context of a clinical investigation, but no specific guidance on the nature, methodological quality and value of different study designs is considered in the MDR.

On the contrary, the type and nature of clinical investigations leading to the approval of drugs, from their laboratory development to widespread clinical use, have been standardized and substantially harmonized on an international basis [2]. There are clear requirements for evidence of safety at early stages, and subsequently for proof of efficacy from RCTs powered for clinical endpoints. Regrettably, clear and harmonized requirements do not yet exist for medical devices [3].

1.1 Deliverable structure

The deliverable 2.3 is articulated as a brief overview of the current landscape of clinical investigations that may be employed for the evaluation of the performance and safety of high-risk medical devices. The concepts reported in the deliverable were discussed in the consortium through a series of on-line meetings and during the stakeholder workshop organized in Brussels on the 21st of November 2024 (M32) during which these initial proposals to build a hierarchy of clinical study designs were discussed with invited clinical study design experts and regulators. Following the event, the consolidated version of the proposed hierarchy has been iteratively refined until the end of the project. Further, the CORE-MD final recommendations for a hierarchy of clinical evidence for high-risk medical devices have been more extensively elaborated in the Deliverable D4.3.

2 Hierarchy of clinical evidence

Conventionally, study designs are graded in a hierarchy based on their inherent risk of bias. Bias in clinical research is defined as a systematic error that undermines the validity of the results of clinical investigation. The concept of the "pyramid of evidence" (see Figure 1), which provides a grading to different study designs based on their inherent risk of bias, has become well known in medicine and clinical research [4]. RCTs are at the top of the pyramid and are considered the cornerstone of modern evidence-based medicine [5]. Randomly assigning participants to different therapeutic strategies in an RCT minimizes sources of bias and allows inference of causality between treatments or interventions and their clinical outcomes [6][7].

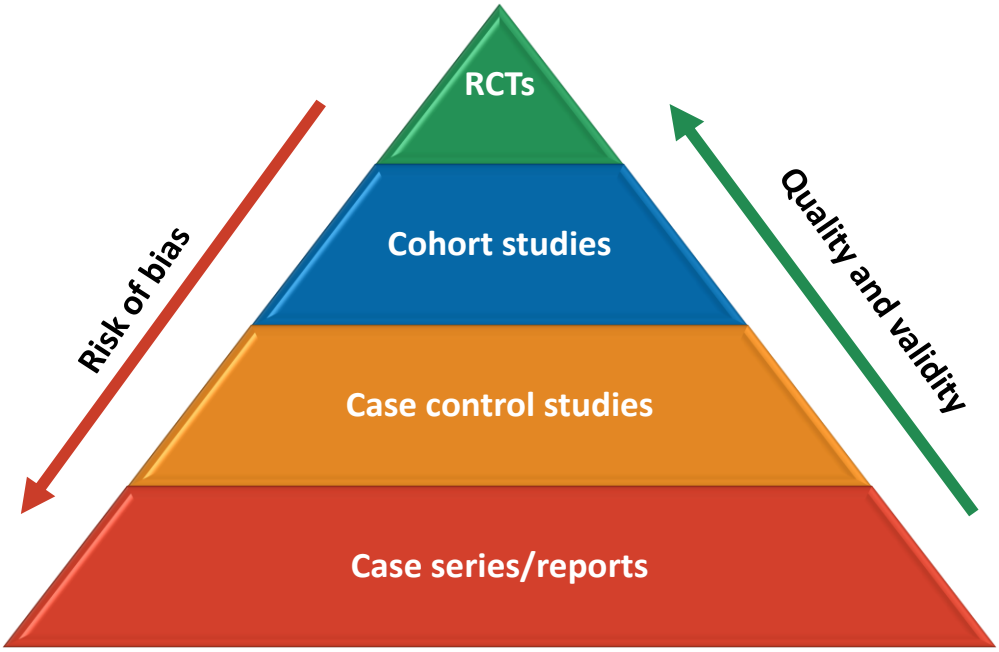

Figure 1. The pyramid of clinical evidence

The pyramid of evidence provides a simple hierarchy of study designs based on their inherent risk of bias.

For high-risk medical devices, an important aspect to consider is that the most appropriate study design may be different depending on the stage of development. Indeed, a high-risk medical device should be evaluated progressively with study designs appropriate to each stage of development and throughout its entire lifecycle. Moreover, optimal study designs may be different according to the category of the device (e.g., established versus innovative device).

3 Clinical investigation of medical devices throughout their lifecycle

Different frameworks have been proposed as guidance for the evaluation of complex interventions and/or high risk medical devices, from their early stages to clinical approval and post-approval phases [8]. For example, the IDEAL framework and its extension to medical devices (IDEAL-D) support a multi-stage process aiming at standardizing the clinical development of complex interventions including those performed using high-risk medical devices [9][10].

Based on existing models of multi-stage development, a high-risk medical device should be evaluated progressively with study designs appropriate to each stage of development (Figure 2) [10][11]. Proving the feasibility, biocompatibility, safety and potential value of a completely new device is necessary in preclinical studies (such as computer simulations, and animal models) before conducting first-in-human studies [12][13][14]. During early clinical testing, small case series (e.g. in 20-50 patients) reporting early feasibility, procedural safety, and expected/unexpected adverse events are important. Refinements to the technical components of a device or its implantation technique may be necessary to improve the performance and safety of the intervention. During these early phases, learning curves and the technical complexity of the intervention should be assessed [15].

At a later stage, larger studies may be conducted to corroborate the feasibility and safety of the procedure and to provide initial hints on comparative efficacy – such as retrospective case-control studies, historical cohorts, and studies using performance goals and objective performance criteria. However, all clinical investigations that compare interventions without randomizing patients remain at substantial risk of bias. Their findings should not be considered as compelling evidence of efficacy and safety. The results of non-randomized studies should be used primarily to inform the design of RCTs, anticipating rates of relevant clinical outcomes for power/sample size considerations. There have been many prominent instances when the results of observational studies have deviated substantially from the findings of RCTs. Single-arm studies are unhelpful when comparing long-term efficacy of alternative devices.

When the technical iteration of a high-risk device and/or the technique for its use are considered sufficiently mature to allow reproducible outcomes, then RCTs (from small to large) should be performed in order to gain definitive evidence on comparative efficacy, clinical benefit and safety. The phases of clinical investigation should culminate in a large simple RCT (see Figure 2). Unlike current practice [16][17], these phases represent an optimal pathway for the clinical investigation of medical devices.

After approval and during the post-market phase, the performance of medical devices should be monitored continuously by systematically collecting and reporting not only objective measures of benefit, but also any device faults, any adverse events related to the device or the procedure, and temporal trends in the incidence of adverse events [1][18]. Medical registries, defined by the International Medical Device Regulators Forum as an “organized system that continuously collects relevant data, evaluates meaningful

outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale", are widely considered to be the optimal approach to collecting data for post-market surveillance. To date, however, their quality, coverage, and designs vary substantially [19][20], and few European device registries include all patients and achieve complete follow-up at a national or international level [21][22].

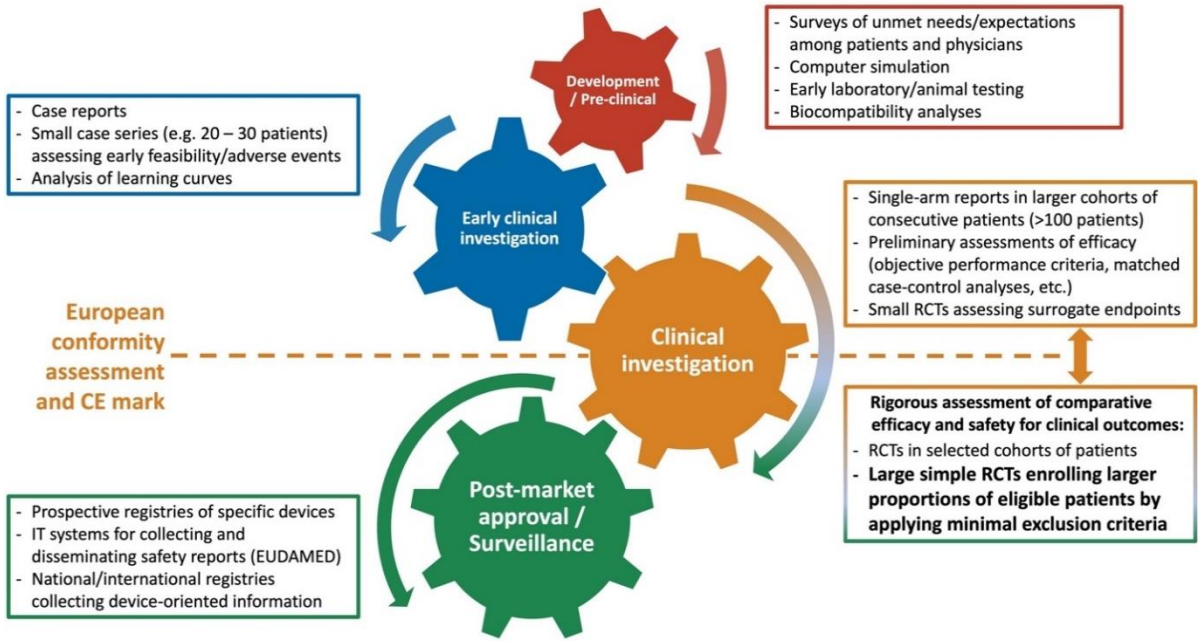

Figure 2. Methods for evaluation and clinical investigation of devices throughout their life cycle

Summary of the principal methods for establishing clinical evidence for new high-risk medical devices, at each stage of their life cycle. In the European Union under the previous medical device directives, regulatory approval (or conformity assessment by a notified body) was often obtained before a pivotal clinical trial had been completed. That may still be appropriate when a new device satisfies an unmet need, but on condition that a large trial or a comprehensive registry is performed within a pre-determined time interval after market access. When a new device is developed as an alternative to effective existing devices, a more rigorous study – and ideally, a large simple randomized controlled trial – should be performed. The variations in timing of CE marking that would result according to these different circumstances is shown by the dotted horizontal line and the vertical arrow.

4 Summary and conclusions

The deliverable 2.3 provides insights on optimal pathways for the clinical investigation of medical devices. Although a hierarchy of study designs is generally accepted in clinical research, optimal study designs for high-risk devices should match the stage of development and the nature of the device (e.g., established versus innovative). RCTs are at the top of the pyramid and are considered the cornerstone of modern evidence-based medicine. In the EU under the previous medical device directives, regulatory approval (or conformity assessment by a notified body) was often obtained before a pivotal RCT had been completed. That may still be appropriate when a new device satisfies an unmet need, but on condition that a large trial or a comprehensive registry is performed within a pre-determined time interval after market access. When a new device is developed as an alternative to effective existing devices, a more rigorous study – and ideally, a large simple RCT – should be performed.

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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.

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

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