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Strengthening Evidence for High-Risk Medical Devices

High-risk medical devices support care for millions of Europeans, yet the public record often falls short of the rigorous clinical evidence clinicians expect before implantation. Reviews conducted by the CORE–MD consortium across cardiology, orthopaedics, diabetes and paediatrics found limited use of randomised trials at approval and substantial delays between device use and publication, highlighting variability and opacity in the evidence base. Against this backdrop, European regulatory texts describe principles but give little practical direction on which study designs should underpin approvals. CORE–MD proposes a structured methodology to guide regulators, manufacturers and investigators, aiming to make clinical evidence clearer, stronger and more predictable across a device's lifecycle.

Evidence Gaps and Regulatory Uncertainty

Analyses of 641 investigations for 114 high-risk devices show modest rates of randomisation at the point of approval with publication often lagging years behind clinical use. In orthopaedics the median interval from first patient inclusion to the first publication reached a decade while registry cohorts comprised a notable share of post-market evidence. For paediatric indications similar scarcity of robust trials was observed. These findings explain why clinicians and patients frequently encounter limited public data on safety, performance and clinical benefits at the time of adoption.

The scale of exposure underscores the stakes. Surveys indicate that around one third of adults in some populations carry implanted metal devices with cardiovascular and orthopaedic technologies dominating high-risk approvals. Despite this prevalence, approval dossiers within Europe can rest on heterogeneous methodologies because current rules emphasise broad principles rather than specifying designs or thresholds that constitute sufficient clinical evidence. Guidance documents reference stages and concepts but offer little in the way of ranked methodologies or clear expectations for particular device types. This leaves manufacturers to choose designs and notified bodies to judge sufficiency without shared detailed benchmarks, fostering variation and unpredictable outcomes.

CORE–MD's review of European guidance confirms the gap. While some international regulators present explicit hierarchies of designs, European materials often refer generically to results of clinical investigations without defining methodological standards. In practice EU rules preclude notified bodies from advising manufacturers on acceptable designs in advance, further complicating convergence on best practice. Collectively these structural features sustain the risk that high-risk devices may reach the market without definitive pre-market clinical investigations.

Must Read:** **AI Diagnostics: Promise, Risk and the Path to Safer Care

Recommended Designs and Statistical Standards

CORE–MD sets out a four-stage framework for clinical investigations: initial, early, confirmatory and long-term studies. The preferred design for confirmatory evaluation is a randomised controlled trial comparing the device with a state-of-the-art active alternative and using patient-relevant clinical endpoints. When no effective active treatment exists and placebo effects are plausible, a sham intervention may be considered with strict ethical safeguards and enhanced informed consent. Across designs blinding of endpoint assessment is emphasised, including PROBE-style approaches in open-label settings to limit bias.

Statistical guidance aims to align power, endpoints and interpretation with patient-relevant outcomes. Trials should be adequately powered, typically at least 80 % with two-sided testing, and follow-up must be sufficiently long and complete to capture safety signals. Where surrogate endpoints are necessary, practical or scientific justification is required. Illustratively, expert advice for coronary stents suggests that surrogate-based studies may enrol in the low hundreds of patients whereas trials powered for clinical endpoints may require enrolment in the low

thousands. These figures are presented as context for planning rather than universal rules with device-specific considerations determining exact sample sizes.

Non-inferiority and equivalence trials should apply realistic evidence-supported margins. CORE–MD advises interpreting results on a relative scale, recommending that non-inferiority be judged using the upper bound of a two-sided 95 % confidence interval for a relative effect measure with the example threshold that a device be unlikely to be more than 15 % worse than control for unfavourable outcomes. This orientation supports comparability across studies and avoids misleading conclusions when baseline risks are low.

Efficiency and scale can be improved by embedding trials in electronic platforms and registries. Large simple randomised trials including registry-based designs are encouraged once device design is stable. These approaches can accelerate recruitment, reduce costs and broaden generalisability. When RCTs are infeasible well-designed cohort studies can provide supportive evidence provided they incorporate independent adjudication, robust control of confounding, long and complete follow-up and, where appropriate, objective performance criteria as benchmarks. Across all stages transparency is required: pre-registration of protocols and analysis plans, public reporting of objectives and methods, adherence to FAIR principles for data and pre-specification and justification of any protocol amendments.

Tailored Pathways for Breakthrough and Established Markets

CORE–MD differentiates pathways according to clinical context. For breakthrough or orphan devices addressing serious unmet needs without alternatives, earlier approval may be considered after the early study phase contingent on mandatory post-market confirmatory evidence and long-term follow-up. Three conditions should be met beforehand: independent confirmation of unmet need, use for a serious disease or condition and absence of approved alternatives. Historical control comparisons are generally discouraged except in life-saving scenarios where no prior options exist. For children early approval with limited evidence may be acceptable when adequately powered prospective studies are impossible with expert and family involvement central to ethical decision-making.

For device types with existing therapeutic options approval should normally follow confirmatory investigations. New devices intended for indications with available alternatives should demonstrate at least comparable safety and effectiveness in head-to-head comparisons against the current state of the art. Iterative modifications must satisfy equivalence provisions or undergo new investigations. This default expectation for randomised comparison is presented as ethically and methodologically sound even if difficult, to prevent the introduction of devices that underperform established options.

Long-term evidence is a core pillar of the framework. Follow-up should reflect the intended lifetime of the device and capture late adverse effects such as loosening of orthopaedic implants beyond ten years. Registry inclusion is expected to be comprehensive with a target of enrolling more than 95 % of eligible patients and cohorts should be representative and geographically broad. While conditional approval mechanisms are not embedded in the European framework, certificates can carry conditions though these have been used sparingly. The consortium’s proposals are being considered by European regulators as they revise guidance and explore reforms to improve transparency, proportionality and global alignment.

CORE–MD’s proposals aim to align clinical evaluation of high-risk medical devices with the expectations of patients and professionals by elevating methodological standards and making regulatory requirements more predictable. A four-stage lifecycle approach, a default to comparative randomised designs where feasible, clear statistical principles and robust long-term registry follow-up together provide a coherent pathway to strengthen clinical evidence. Implementation by European regulators could reduce uncertainty in approvals, prioritise patient-relevant outcomes and support safer more effective adoption of high-risk devices across health systems.

Source: The Lancet Regional Health: Europe

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