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Peer Review

Review of: "Integrity of Clinical RCTs: Safeguarding Trust, Evidence, and Patient Welfare"

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The article „Integrity of Clinical RCTs: Safeguarding Trust, Evidence, and Patient Welfare" by Ulrich Mansmann provides a comprehensive, very valuable overview of quality aspects of clinical RCTs. It pleads for the consideration of the whole life cycle of a study with all its issues and tools, including also less obvious ones (such as post-publication reviews, missing value, and sensitivity analyses). In particular, one focus is on the estimand framework, which, in addition to PICO, considers the details of the estimation-generating process, such as how intercurrent events are handled. It gives a bird's-eye view rather than a technical description of the toolkits. For example, it does not mention technical terms such as intention-to-treat or attrition bias. The general point is made very clear: Integrity goes beyond the fulfilment of some checklists but requires an according culture.

Apart from straightforward reminders about various quality standards, it also gives single thoughts worth reflecting on. Just a few examples: "Interpretive integrity also requires balanced reporting of benefits and harms." – "The statistical analysis should implement the trial question, not quietly replace it." – "Negative trials are also prone to spin: the tendency to shift attention from a non-significant primary endpoint to favourable secondary, exploratory, per-protocol, subgroup, biomarker, or safety endings." The article also provides links to important institutions, particularly helpful for younger scientists.

Acknowledging this, some more discussion about certain aspects would have been interesting, in particular about the costs or even pitfalls regarding some of the tools (e.g., dangers of post-publication review – would they need reviewing for themselves?). In general, highest quality and integrity are paramount; it is easy to call for maximum standards, but nevertheless, they may come at a price: more effort, more documentation, and so on. This could also mean that fewer studies might be conducted if the

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integrity ambition might overdo it, or that standards get bypassed. For example, regarding documentation: how thorough is thorough enough? It would be helpful to read about potential disadvantages or possible trade-offs, or whether the benefits of the integrity standards outweigh all costs or dangers. I fully trust in the validity of all claims of the article; I would just appreciate a discussion about the actual practicability and what it would mean for those who conduct studies.

Declarations

Potential competing interests: No potential competing interests to declare.