

Editorial

ARE RANDOMIZED CONTROLLED TRIALS AS GOLD STRANDARD FOR HIGH LEVEL EVIDENCE A PRAGMATIC APPROACH IN THE ERA OF PRECISION MEDICINE AND REAL-WORLD EVIDENCE

Binafsha Manzoor Syed

Medical Research centre, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

Correspondence:

Binafsha Manzoor
Syed, Medical Research
Centre, Liaquat
University of Medical
and Health Sciences,
Jamshoro Pakistan

Email:

Binafsha.syed@lumhs.edu.pk

du.pk

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ABSTRACT:

Randomized controlled trials (RCTs) have been considered as the gold standard for evaluating medical interventions due to their robust methodology, limited introduction of bias, and strength in establishing strong evidence to show better effect of a treatment option. However, the evolving landscape of healthcare—marked by precision medicine, digital health technologies, and expanding access to real-world data—has exposed important limitations in the traditional dominance of RCTs. These include issues of generalizability, cost, ethical constraints, and limited applicability in heterogeneous patient populations, particularly in low- and middle-income countries. Concurrently, the emergence of real-world evidence, pragmatic trials, and adaptive designs has introduced complementary paradigms that challenge the exclusivity of RCTs in evidence hierarchies. This editorial provides a critical and expanded appraisal of the role of RCTs in contemporary medicine, examining their enduring strengths alongside their limitations, and highlighting the need for an integrated, context-sensitive approach to evidence generation.

Keywords: Phase III clinical trials, Randomized Control Trials, hierarchy of scientific evidence, clinical research
INTRODUCTION

The importance of randomized controlled trials (RCTs) in clinical research is deeply embedded in the philosophy of evidence-based medicine. Since their formalization in the mid-20th century, RCTs have provided a robust methodological framework for minimizing bias through randomization, blinding, and controlled comparisons. Thus, required for approvals of regulatory authorities for use of drugs in clinical practice. This design enables researchers to isolate the effect of an intervention with a high degree of internal validity, making RCTs indispensable for regulatory decision-making and clinical guideline continue to be developed on RCT driven evidences. Major global institutions, including the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA), continue to rely on RCT-derived evidence as the cornerstone for approving therapeutics and shaping public health policies. However, the concept of RCTs as the unquestioned gold standard is increasingly being scrutinized. Modern medicine is no longer confined to controlled experimental environments; it operates within complex, dynamic health systems characterized by diverse patient populations, variable resource availability, and rapidly evolving technologies.

Validity-generalizability of results in strict controlled environment versus really world patients

RCTs are optimized for internal validity, ensuring that observed outcomes can be attributed with confidence to the intervention under investigation. Yet this rigor often comes at the expense of external validity. Strict eligibility criteria frequently exclude patients with comorbidities, polypharmacy, advanced age, or atypical disease presentations. As a result, trial populations may not accurately reflect the patients encountered in routine clinical practice. This disconnect has tangible consequences. Clinicians are often required to extrapolate findings from idealized trial settings to complex real-world scenarios, where treatment responses may differ significantly. For instance, oncology trials frequently enroll younger, fitter patients, whereas real-world cancer populations include frail individuals with multiple comorbidities. The resulting evidence gap raises concerns about the applicability of RCT findings across diverse healthcare settings. Also the spectrum of side effects is much wider in real world patients as compared to the controlled carefully selected trial population. Thus generalizability of trials of needs to be interpreted carefully. However, still considering it as the highest level of evidence in the given scenario.

Economic and financial Constraints

The financial burden associated with conducting RCTs is substantial. Large multicenter trials require extensive infrastructure, regulatory compliance, monitoring systems, and long follow-up periods. These requirements limit the feasibility of RCTs in resource-constrained environments, including many institutions in low- and middle-income countries. Establishment of Clinical Trial Units with approval from regulatory authorities is itself an expensive undertaking. For academic centers such as those in Pakistan, the reliance on externally funded RCTs may inadvertently skew research priorities toward globally driven agendas rather than locally relevant health challenges. Consequently, diseases with high regional burden but limited commercial interest may remain under-investigated. This imbalance underscores the need for alternative evidence generation strategies that are both cost-effective and contextually relevant.

Ethical Complexities

Ethical considerations further complicate the implementation of RCTs. The principle of clinical equipoise—genuine uncertainty regarding the comparative effectiveness of interventions—is a prerequisite for ethical randomization. However, in rapidly evolving fields such as oncology or during public health emergencies like COVID-19, maintaining equipoise can be challenging. In life-threatening conditions, withholding a potentially beneficial therapy for the sake of randomization may be ethically contentious. Similarly, patient preferences and physician judgment increasingly influence treatment decisions, potentially undermining recruitment and adherence in RCTs. These challenges necessitate more flexible and patient-centered research designs.

The Rise of Real World Evidence

The digital transformation of healthcare has facilitated the generation of vast amounts of real-world data through electronic health records, insurance databases, disease registries, and wearable technologies. Real-world evidence, derived from these sources, provides valuable insights into treatment effectiveness, safety, and long-term outcomes in routine clinical practice. Unlike RCTs, real world evidence captures the heterogeneous set of patient populations and healthcare delivery systems. It is particularly useful for post-marketing surveillance, rare adverse event detection, and evaluation of interventions in populations typically excluded from trials. Regulatory bodies including FDA, have increasingly recognized the value of real world evidence in supplementing traditional clinical trial data. However, real world evidence is not without limitations. Observational data are inherently susceptible to confounding, selection bias, and data quality issues. These issues cannot be sorted without having proper randomization and strict selection criteria.

Precision Medicine and the Fragmentation of Evidence

The advent of precision medicine challenges the traditional RCT paradigm by focusing on individualized treatment strategies based on genetic, molecular, and phenotypic characteristics. In such contexts, the concept of a treatment effect becomes less meaningful without considering molecular parameters. For example, targeted therapies in oncology may be effective only in small, biomarker-defined subgroups, making large-scale randomization impractical. This necessitates alternative designs, including single-arm trials with historical controls, while these approaches offer practical solutions.

For healthcare systems in LMICs, the debate is not merely academic but deeply pragmatic. The exclusive reliance on RCTs may limit the generation of locally relevant evidence due to financial, infrastructural, and logistical constraints. Conversely, well-designed observational studies and pragmatic trials can provide actionable insights tailored to regional disease burdens and healthcare realities. By embracing methodological diversity and encouraging high-quality non-RCT research, they can facilitate evidence generation that is both scientifically robust and contextually meaningful. This includes promoting standardized reporting guidelines, fostering interdisciplinary collaboration, and prioritizing research with direct clinical and policy relevance.

CONCLUSION

Randomized controlled trials remain a foundational pillar of clinical research, offering unmatched rigor in establishing high level of clinical evidence. However, their designation as the singular gold standard is increasingly incongruent with the complexities of modern medicine. The future of evidence-based practice lies in a pluralistic, integrated approach that combines the strengths of RCTs with the complementary insights of real-world evidence and innovative trial designs. This requires moving beyond rigid hierarchies toward a more nuanced, context-sensitive paradigm that prioritizes relevance, inclusivity, and methodological rigor in equal measure.

Conflict of Interest

Author declare no conflict of interest.