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Editorial

The Changing Face of Clinical Trial Design

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1. Introduction

Randomised clinical trials (RCTs) provide the most reliable means of evaluating the effects of medical interventions. Their strength lies in their ability to minimise bias and permit causal inference through the random allocation of treatment [1]. Despite advances in observational data collection and analysis, only randomisation can reliably minimise both known and unknown confounding. Target trial emulation seeks to reduce methodological biases by designing observational analyses to emulate the protocol of a hypothetical RCT [2]. However, treatment allocation remains non-random and residual confounding cannot be eliminated. In this editorial, we first reaffirm the principles that underpin credible RCTs before considering how emerging approaches are expanding the RCT toolkit while introducing new methodological challenges.

2. Fundamental Principles of RCTs

Most therapeutic advances confer modest rather than dramatic benefits, making well-designed and adequately powered trials essential for distinguishing genuine effects from chance findings. Nevertheless, inadequate recruitment, lower-than-expected event rates, and poorly chosen outcomes may prevent studies from providing definitive answers [1].

A critical component of trial design is the selection of appropriate endpoints, particularly the primary endpoint on which the significance and conclusions of the trial depend. Such outcomes should be meaningful, measurable, and sensitive to the anticipated effects of the intervention. Separating efficacy (benefit) from safety (harm) can help with interpretation and generalisation [3].

Mortality is regarded as a particularly robust clinical endpoint because it is objective, clinically important, easy to measure and less susceptible to bias [4]. However, in many settings, interventions influence only a proportion of total deaths. As a result, all-cause mortality may be a relatively insensitive measure of treatment effect compared with cause-specific mortality and often requires substantially larger sample sizes than more directly affected outcomes. All-cause mortality is most clearly an appropriate primary endpoint when a high proportion of participants are expected to die of the disease under study (e.g., late-stage cancer or acute interventions with short-term outcomes) [3]. Furthermore, many interventions produce benefit without necessarily altering overall survival in the time scale of the trial. Treatments may reduce symptoms, delay disease progression, or enhance quality of life.

Composite primary endpoints are commonly used to improve statistical efficiency. Composite outcomes are particularly common in cardiovascular medicine, where studies use various combinations of cardiovascular death, myocardial infarction, stroke, hospitalisation, and other clinically relevant events. Despite their practical advantages, composite endpoints present some interpretive challenges. Individual components often differ in clinical importance, and the overall treatment effect may be driven by less severe outcomes. This can complicate their interpretation and potentially exaggerate perceptions of benefit. Careful examination of the contribution of each component to an overall effect is therefore essential [5].

Traditional time-to-event analyses remain central to contemporary clinical research. Kaplan-Meier survival curves provide intuitive visual representations of event occurrence over time, while log-rank tests are used to compare outcomes between treatment groups. Cox proportional hazards models complement this approach by estimating the magnitude of treatment effects and allowing adjustment for relevant patient characteristics.

Nevertheless, these methods have limitations. They focus on time to first event, thereby not accounting for subsequent events that may contribute substantially to overall disease burden. Consequently, attention is being directed towards methods that account for all relevant events, such as negative binomial and joint frailty models, particularly in diseases characterised by repeated hospitalisations [6].

Another challenge relates to the proportional hazards assumption underlying Cox regression. Treatment effects do not always remain constant throughout follow-up. Some interventions produce immediate benefits that diminish over time, others may be associated with early hazards followed by later benefits, while some may require prolonged exposure before demonstrating effectiveness. In such circumstances, hazard ratios may not fully describe the complexity of treatment effects and may be more difficult to interpret. Alternative measures such as restricted mean survival time, do not rely on the proportional hazards assumption and may provide a more intuitive summary of the intervention effect [7].

Beyond the choice of statistical methods, emphasis needs to be placed on defining precisely the treatment effect

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a trial seeks to estimate. The International Council for Harmonisation (ICH) E9(R1) estimands framework encourages investigators to define explicitly the treatment effect of interest and how intercurrent events such as treatment discontinuation or death should be handled [8]. Bayesian methods require prior estimates of treatment effect and can be statistically efficient but have not found widespread use [9].

3. Recent Innovations in RCT Design and Analysis

Alternative approaches have emerged, offering potential solutions to limitations associated with conventional RCT design and analyses. Among the most influential is the win ratio which builds on the earlier Finkelstein-Schoenfeld method and analyses outcomes according to a predefined hierarchy of clinical importance [10]. More important events, such as death, are considered before less severe outcomes such as hospitalisation. This approach may more closely reflect clinical priorities, particularly when severe outcomes are uncommon, and may improve statistical efficiency in settings where the treatment effect is concentrated in non-fatal components [11].

However, interpretation of the win ratio is less intuitive than hazard ratios and remains dependent on the chosen hierarchy of outcomes and analytical approach. Different hierarchies may produce different conclusions, while results may also be influenced by follow-up duration, censoring, and the handling of tied comparisons. Furthermore, the timing or durability of treatment effects is not captured as directly as in traditional survival analyses.

Non-inferiority trials have also become more widely used. In many situations, new treatments are introduced not because they are expected to be more effective than existing therapies, but because they may offer advantages in safety, tolerability, or cost. However, interpretation of such trials can be challenging. Selection of the non-inferiority margin requires both statistical and clinical judgement and is typically informed by evidence regarding the effect of the active comparator relative to placebo. The choice of non-inferiority margin remains partly subjective, and biases arising from non-adherence or loss to follow-up may favour conclusions of non-inferiority. Although intention-to-treat analysis is fundamental in superiority trials because it preserves the benefits of randomisation and reduces bias introduced by treatment non-adherence or post-randomisation exclusions, non-inferiority trials typically require both intention-to-treat and per-protocol analyses because non-adherence and protocol deviations may bias results towards non-inferiority. As such, findings require careful scrutiny and should not be interpreted as evidence of equivalence nor do they establish superiority unless superiority testing has been pre-specified and appropriately conducted [12].

The increasing use of electronic health records, clinical registries, and digital technologies is further reshaping clinical research. These approaches can facilitate recruitment, outcome ascertainment, and long-term follow-up while reducing trial costs and operational complexity [13]. Registry-based RCTs have demonstrated how existing national clinical registries can be used to efficiently identify, randomise, and follow participants while maintaining methodological rigour [14]. However, registry-based and digitally enabled trials also have limitations, including variable data quality, incomplete outcome capture, and the potential for selection bias, all of which require careful consideration during trial design and interpretation.

Adaptive and platform trial designs represent another important advance. Platform trials allow multiple therapies to be assessed simultaneously within a common infrastructure, whereas adaptive designs permit prospectively planned modifications to aspects of a trial based on accumulating data. Interventions may be added, modified, or discontinued according to accumulating evidence, increasing efficiency and accelerating evidence generation. The success of these approaches during the coronavirus disease 2019 (COVID-19) pandemic demonstrated that high-quality randomised evidence can be generated rapidly without compromising scientific rigour [15]. These designs also introduce challenges, including the management of non-concurrent controls, control of type I error across multiple comparisons, and potential biases associated with open-label treatment assessment.

Importantly, these innovations do not replace the principles that have long underpinned reliable RCTs. Whether a trial is conventional, adaptive, registry-based, or digitally enabled, robust randomisation, clinically meaningful endpoints, complete follow-up, adequate statistical power, and unbiased analysis remain essential prerequisites for trustworthy conclusions. For practising clinicians, critical appraisal increasingly requires understanding not only whether a trial is randomised, but also how treatment effects are defined, analysed, and reported, particularly when approaches such as non-inferiority designs, win-ratio analyses, or recurrent-event methods are employed.

4. Conclusion

The changing face of clinical trials therefore reflects evolution rather than revolution. Randomisation remains the cornerstone of reliable evidence generation, but the methods used to design, conduct, and analyse trials continue to evolve. Greater emphasis on endpoints that better reflect both clinical and patient priorities, innovative analytical approaches, and trial designs is helping researchers address important clinical questions.

The future of clinical trials is unlikely to be defined by a single statistical method or trial design. Rather, it will be characterised by the integration of rigorous randomised evaluation with more meaningful endpoints, efficient trial infrastructure, and analytical approaches that better reflect clinical priorities and disease burden, ultimately improving the relevance and applicability of evidence to everyday clinical practice.

Key Points

• RCTs remain the most reliable method for evaluating treatment effects and minimising bias.

• Careful primary endpoint selection is essential to ensure outcomes are clinically meaningful, and sensitive to therapeutic effects.

• Time-to-event analyses remain important but may not adequately capture all aspects of the effect of interventions.

• Emerging approaches such as the win ratio seek to better reflect clinically important treatment effects.

• Adaptive, registry-based, and digitally enabled trial designs are increasing the efficiency and applicability of evidence generation while preserving the fundamental principles of robust randomised evaluation.

Availability of Data and Materials

Not applicable.

Author Contributions

MGZ and JA conceptualized the editorial. MGZ drafted the manuscript. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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