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EDITORIAL

Randomized Clinical Trials vs. Observational Studies: which is best for your research question?

Ensaios Clínicos Randomizados vs. Estudos Observacionais: qual é o melhor para a sua pergunta de pesquisa?

Fernando Zanela da Silva Arêas[1,2]

[1] Baylor Scott and White Research Institute. Dallas, TX, USA.

[2] Laboratorio de Neuroreabilitação e Neuromodulação,Programa de Universidade Federal do Espírito Santo. Vitória, ES, Brazil.

Correspondence:
fernandozanela@hotmail.com

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Choosing the best study design for clinical research goes far beyond following a rigid hierarchy of evidence. Although Randomized Clinical Trials (RCTs) are widely regarded as the gold standard in clinical research, the choice between RCTs and observational studies should primarily be guided by the research question, ethical considerations, feasibility, and the nature of the outcomes assessed[1].

As discussed by Concato et al, we should not treat the evidence hierarchy as a rigid pyramid in which RCTs are always superior to observational studies. Well-designed studies — whether randomized or observational — can provide reliable evidence if they are properly planned to address the specific research question. In many cases, observational studies produce results similar to RCTs, as demonstrated by Concato et al. and Ross et al, who compared different research designs and found a high degree of concordance in their overall conclusions.

The main difference between RCTs and observational studies lies in the process of randomization[4]. Randomization theoretically allows for balanced groups regarding known and unknown confounding factors, increasing internal validity[5]. However, RCTs typically employ strict inclusion and exclusion criteria, reducing sample representativeness and thus external validity[6]. RCTs are highly valuable when testing the efficacy of an intervention under controlled conditions, but they do not always reflect real-world clinical practice. In contrast, observational studies include more heterogeneous populations and have greater adherence to real-world clinical practice[7]. They are especially useful in investigating prognosis, incidence, prevalence, and long-term safety — areas frequently neglected by RCTs due to time and cost limitations. For example, in chronic diseases, observational studies have been essential for understanding long-term functional trajectories and the influence of comorbidities[8].

It is important to emphasize that observational studies, by nature, are not the most suitable for evaluating the effect of interventions, as they are more susceptible to bias. However, in several areas of medicine, carrying out RCTs is particularly challenging or even impractical. This is the case in fields such as rehabilitation, physical therapy, palliative care, mental health, rare diseases, and emergency medicine[9]. In these contexts, ethical issues, difficulties in randomizing patients, highly individualized interventions, or the impossibility of blinding limit the execution of RCTs. For example, in rehabilitation, treatments often need to be tailored to each patient's needs and limitations, making standardization almost impossible. In palliative care, ethical considerations related to patient well-being and consent also challenge the execution of rigorous RCTs. Thus, observational studies play a fundamental role in gathering evidence in these areas[9].

The absence of randomization makes observational studies more susceptible to bias and confounding factors, highlighting the importance of methodological quality[2]. Just as a poorly designed RCT can overestimate treatment effects, an observational study conducted with rigor can provide reliable evidence by adequately adjusting for confounding factors[4]. Furthermore, many therapeutic strategies considered "evidence-based" have never been evaluated in prospective RCTs, in part because it would be unethical to deny established treatments in a placebo-controlled trial. For instance, a recent publication in BMC Anesthesiology by Trentino et al. reviews the strengths and weaknesses of observational studies in the context of transfusion strategies and concludes that, when comparing results from different study designs, attention must be given to methodological details rather than simply the study type label[10].

Historic examples of divergence between RCTs and observational studies highlight the importance of context and methodological rigor. The bisphosphonates case for breast cancer prevention showed how observational studies suggested a benefit not confirmed by RCTs, likely due to the "healthy user bias," which can distort results in non-randomized research[3,11]. Therefore, we must ask whether it still makes sense to speak of a rigid "hierarchy" of evidence. A more appropriate model may be a circle, in which each study type occupies its place according to the research question, clinical context, and methodological limitations. The reliability of the evidence does not depend on the study design label but on its applicability, validity, and methodological rigor.

In conclusion, both RCTs and observational studies are valuable sources of scientific knowledge, each with its strengths and limitations. The best design is the one that, in the most ethical and effective way, answers the research question. Instead of debating which is superior, we should reflect on how these designs complement each other and, together, promote better clinical decision-making.

COMPARATIVE OVERVIEW: RCTS VS. OBSERVATIONAL STUDIES

To guide your study design choice, consider the following recommendations:

- **Internal Validity (Cause-Effect):**
  - **RCTs:** High, due to randomization balancing known and unknown confounders.
  - **Observational Studies:** Lower, more susceptible to bias and confounding; requires rigorous statistical adjustment.
- **External Validity (Generalizability to Real World):**
  - **RCTs:** Lower, due to strict inclusion/exclusion criteria and controlled conditions.
  - **Observational Studies:** Higher, includes more heterogeneous populations and reflects real-world practice.
- **Feasibility & Ethics:**
  - **RCTs:** Can be costly, time-consuming, and ethically challenging (e.g., when denying established treatments, in rare diseases, or in highly individualized interventions).
  - **Observational Studies:** More feasible for long-term outcomes, rare events, and situations where randomization is impractical or unethical.

- **Primary Use Cases:**
  - **RCTs:** Best for testing the *efficacy* of an intervention under controlled conditions.
  - **Observational Studies:** Best for investigating *prognosis*, *incidence*, *prevalence*, *risk factors*, *long-term safety*, and understanding complex, real-world scenarios.
- **Bias Susceptibility:**
  - **RCTs:** Less susceptible to selection bias; potential for performance and detection bias if not properly blinded.
  - **Observational Studies:** Highly susceptible to selection bias, confounding, and healthy user bias.
- **Reliability of Evidence:**
  - **Both:** Reliable evidence depends on **methodological rigor**, **applicability**, and **validity** to the specific research question, not solely on the study type label.

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