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Pragmatic clinical trials

Drug use in clinical practice often varies from that seen in controlled clinical trials. Even though these trials are conducted in normal clinical settings, the type of patients enrolled and the approach to their management may not accurately reflect the varying and complex diversity of clinical practice. While randomised controlled trials provide necessary high-quality information about the risks and benefits of medical interventions, many trials have limited application to clinical practice. Most randomised controlled trials are efficacy trials and involve homogeneous patient populations, blinded treatment assignments for both patients and investigators, and follow carefully defined treatment regimens that ensure a high degree of patient compliance. Furthermore, many studies compare an active drug against a placebo to determine efficacy, but this offers no information to health-care decision makers, who may need to determine which of a range of treatments is best.

Because of concerns over how applicable these results may be to real-world clinical practice, and the ongoing need to improve the quality and value of healthcare, there is increasing attention being paid to "pragmatic" clinical trials. These studies are designed specifically to answer the questions faced by decision-makers, patients and clinicians. A pragmatic clinical trial is characterised by comparisons of clinically relevant interventions, recruitment of patients from a diverse range of practices, inclusion of a diverse range of study participants, and examination of a broad range of outcomes.

There are numerous examples of outcomes that have varied from those expected when a new drug or drug practice that has demonstrated successful outcomes under the conditions of a randomised controlled trial have then been implemented in clinical practice. The RALES study resulted in the rapid uptake of spironolactone as an adjunct to heart failure after the study demonstrated an impressive 30% decrease in mortality compared to placebo. Five years later, Canadian investigators demonstrated a marked increase in hyperkalaemia-related hospital admissions, with hyperkalaemia-associated morbidity and mortality, associated with the increased spironolactone use.

More recently, the release of the anticoagulant dabigatran into general practice in Australia has led to an unexpected series of bleeding events, characteristically in patients with poorer renal function. It is notable that many studies exclude patients with kidney function <30ml/min or have a limited number of patients enrolled with poor renal function.

While pragmatic trials are designed to study real-world clinical practice, they are inherently less perfect experiments than efficacy studies. In order to achieve generalizability, they sacrifice a degree of internal validity, and may require greater patient numbers in order to show a clinical difference between treatments. Thus, these limitations of pragmatic trials need to be considered in interpreting the results.

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