Why most randomized controlled trials are irrelevant

And why yours will not be

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How can we make research findings more relevant to our patient populations in primary care? Groups of experts review the evidence to make clinical practice guidelines. This randomized controlled trial (RCT) evidence is limited by strict inclusion criteria that produce idealized patient populations and health care settings. For example, RCTs of asthma, chronic obstructive pulmonary disease, and allergic rhinitis only include 5% to 10% of patients who would be seen in routine care.[1,2] Family physicians provide comprehensive care to individuals and families irrespective of age, sex, disease, comorbidities, and social context. Our patients often have several interacting and competing health problems, all of which require attention and management. Given this, how can we confidently apply these guidelines to our patients and expect the same results?

Here we advocate that clinical practice guidelines should be based on trials conducted in primary care, by or with input from primary care clinicians, to increase their applicability for our patients.

Explanatory versus pragmatic trials

Nearly 50 years ago Schwartz and Lellouch wrote that trials lack applicability beyond the "laboratory" environment: "Most trials done hitherto have adopted the explanatory approach without question; the pragmatic approach would often have been more justifiable."[3]

Explanatory trials answer the question "Can this intervention work under ideal conditions?"[4] These studies measure the effects of defined interventions applied to select groups under optimal circumstances[5] and give the intervention under evaluation the "best chance to demonstrate a beneficial effect."[4] However, these ideal conditions are rare in the primary care setting.

Pragmatic trials answer the question, "Does this intervention work under usual conditions?"[4] These studies are carried out in usual-care, "real-world" settings, where the participants in the trial are similar to the complex patients with comorbidities that we would see in daily practice. Given that these conditions are common, such studies accurately inform clinical, health service, and policy decisions.

Trade-offs?

It has been suggested that there are trade-offs between internal and external validity in choosing pragmatic over explanatory trial designs. Godwin et al wrote that "the danger of pragmatic trials is that internal validity may be overly compromised in the effort to ensure generalizability."[6] *Internal validity* refers to the lack of bias, or systematic error, and can be thought of as accuracy and reliability of the results, whereas *external validity* refers to generalizability, or the relevance of the results to patients in other settings. When we read a report of an RCT, the most important thing to us should be that the results are unbiased and relevant to our patients.

We believe there are no trade-offs in using one design over the other when each is used to answer the appropriate question. As pragmatic trials generally have more heterogeneous groups of patients, practitioners, and sites, they might have wider confidence intervals than explanatory trials and thus slightly less precision. However, if both trial designs are randomized, confounders (variables outside of the study that might affect the outcome of interest) are dealt with similarly and thus there is no increased risk of bias with pragmatic trials. Lack of precision is not the same as bias, and so we would argue that internal validity is not reduced in pragmatic trials. The reason this misconception has arisen is that pragmatic trials often reveal that a given intervention is less effective under usual conditions with usual patients than it is under ideal conditions with patients who have a moderate stage of the disease of interest (that is still responsive to treatment) and who are selected to have high adherence to treatment.[7] In fact, this tendency to a lower apparent effectiveness is arguably a more valid assessment of the real-world effectiveness of an intervention than would be achieved in an explanatory trial.

Rise in interest

The idea of pragmatic research has recently been gaining momentum. A PubMed search using the terms *pragmatic* (title or abstract) and *clinical trial* (publication type) revealed 843 articles on this topic published in the past 5 years, of which a third (33%) were published in the past 18 months. Alongside this rise in interest in pragmatic trials was the development and enhancement of the PRECIS-2 (Pragmatic Explanatory Continuum Indicator Summaries 2) tool[4] (originally developed in 2009 and updated in 2015), which supports the design of pragmatic trials, ensuring that the results of trials are applicable and transferrable to the intended users and settings. A full tool kit that explains how to use PRECIS-2 is available at **www.precis-2.org**.

Conclusion

The time has come to critically consider how trials are done and whether the results can be applied to primary care. As our patients and the health system evolve, our research methods must adapt. Family physicians have the distinct advantage of providing care to a range of patients with diverse, often multiple needs. We are best suited to identify the relevant clinical questions and conduct the right trials for our own patient populations whether we work independently, in group practices, or as part of practice-based research networks. Pragmatic trials do not require the burdens of blinding, strict inclusion criteria, or intense follow-up given that they are matching real-world conditions and aim to collect data within usual care.

Nearly 15 years have passed since Ian McWhinney, the "father of family medicine," asked why we as family physicians are doing so little clinical research.[8] The time has come for this to change; we need to contribute to pragmatic trials that answer relevant primary care questions. This is a step toward an exciting new era of primary care research.

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Competing interests
None declared

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