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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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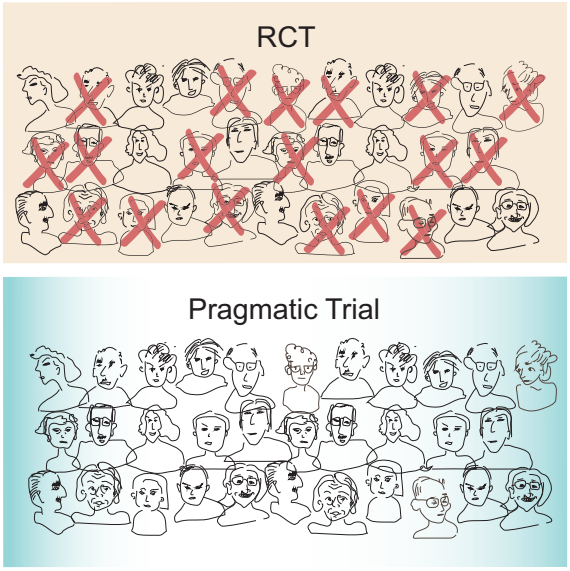
Filling the Evidence Gap
Pragmatic Randomized Controlled Trials in British Columbia



Randomized controlled trials are the cornerstone of medical evidence but there are systematic gaps in this evidence, which need to be filled. This letter discusses some of these gaps, outlines the global need for more pragmatic trials and describes a new British Columbian organization that is attempting to help fill the need.

What is a pragmatic trial?[1]

Most randomized controlled trials (RCTs) are "explanatory" or "efficacy" trials, designed to answer whether a treatment can demonstrate benefit in a select population. Such trials normally compare an intervention to placebo or to another active intervention that may not be standard of care. They also focus on a narrow set of outcomes to which the intervention is targeted. In contrast, "pragmatic" or "effectiveness" trials: 1) examine interventions in a broader population representative of those who will be treated; 2) report outcomes of importance to patients that are intended to capture global benefit and harm; and 3) often compare the intervention in question to standard therapies. Compared to efficacy trials, pragmatic trials are intended to answer the questions that clinicians and patients have regarding therapy.

The need for more representative subjects

Most RCTs use narrow inclusion and exclusion criteria to select the participants most likely to benefit from an intervention and least likely to experience harm (e.g. targeting those at high cardiovascular risk but excluding those with renal insufficiency). This approach maximizes the likelihood of observing benefit. However, this practice also results in many trials excluding subjects similar to the patients most commonly encountered in clinical practice. In a systematic sampling of RCTs published in high impact journals, 38.5% of RCTs excluded older adults, 81.3% excluded individuals with common medical conditions, and 54.1% excluded individuals receiving commonly prescribed medications.[2]

Considering the multiple morbidities present in 71% of diabetics, 82% of osteoarthritics, 83% of chronic obstructive pulmonary disease sufferers, and 92% of those with coronary artery disease,[3] such trials are clearly not representative of real world populations.

Of 20,388 US Medicare patients ≥ 65 years of age, **only 1 in 5 patients discharged from an acute care hospital with a diagnosis of congestive heart failure (CHF) met the criteria for enrollment in 3 landmark trials that guide the treatment of all CHF patients.**[4] As a general rule, although older adults and patients with multiple co-morbidities are often the target of clinical practice guidelines, they are poorly represented in the evidence-generating trials upon which clinical guidelines are based. This is especially important for the frail elderly, who fall into both categories. There are observational data raising questions as to the value of lowering blood pressure and blood sugar in the frail elderly.[5, 6] Such studies are only hypothesis generating but clinical trials in this traditionally understudied population are clearly needed.

The need for better assessment of harm

The use of highly selected and generally healthier patients in efficacy trials increases the likelihood such trials will fail to adequately predict harm in a population with a broader spectrum of disease.

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This was well demonstrated following publication of the Randomized Aldactone Evaluation (RALES) trial when, coincident with increasing use of spironolactone in the general population, rates of hospitalization for hyperkalemia in Ontario rose from 2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001.[7]
The potential for adverse drug-drug or drug-disease interactions increases exponentially with each additional co-morbidity and each additional medication.[8] It is reasonable to question whether the risk-benefit ratio of a new medication might differ meaningfully when that drug becomes the 7th or 8th in use by a patient with 4 co-morbidities as compared to a single drug in an uncomplicated patient.
Efficacy trials at times also employ run-in periods to exclude subjects who do not tolerate the drug, thus reducing the chances of detecting poor tolerability or harm. Given that clinical trials place less emphasis on the evaluation of adverse effects than on primary outcomes[9], and given that adverse drug reactions are so varied in presentation (often mimicking medical diseases[10]), harmful effects of drugs may not be detected until years after a drug is approved for use.

The need for patient-oriented outcomes that matter

Much of the evidence in support of common interventions is based on surrogate outcomes such as HbA1c. This is problematic since recent studies challenge the assumption that surrogates can reliably predict the effect an intervention will have on "hard" outcomes.[11] For example rosiglitazone lowers HbA1c but increases cardiovascular events.[12] Complex clinical scales come somewhat closer to measuring the patient's experience but these, often arbitrary combinations of clinical signs and symptoms, are also problematic in that their clinical meaning is often difficult to determine. As much as possible, outcome measures should be highly objective (e.g. mortality, disabling stroke, hospitalization, nursing home admission, hip fracture) and resonate with patients and clinicians alike (e.g. falls, cognitive impairment, independence, quality of life).

A British Columbia solution

It is perhaps no surprise that the need for pragmatic trials would resonate with primary care physicians, nor that part of the solution, the BC Pragmatic Trials Collaborative, might arise from their ranks. This grassroots group of family physicians, with members from across the province and sponsorship from the BC Divisions Innovation Fund, believes that "large scale pragmatic trials can be conducted with no impact on physician workflow by using electronic health data, which is already collected on all residents of BC".
For more information visit the website:
https://www.divisionsbc.ca/richmond/BCtrials
The next year will see this group approaching the BC Ministry of Health about the utilization of electronic outcome data for the analysis of their randomized controlled trials. The two trials planned to date are 1) a comparison of the effect of medication minimization in frail elderly with standard care, using primarily mortality and nursing home admission as outcomes and 2) a comparison of morning antihypertensive drug dosing with evening antihypertensive drug dosing using primarily mortality and hospitalization for stroke as outcomes.
The BC Pragmatic Trials Collaborative is actively looking for more members. If you are interested or would like more information go to the website or send an e-mail to BCTrials@DivisionsBC.ca.

B.C. Pragmatic Trials Collaborative
Measuring What Matters

The draft of this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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