

How Canada can better embed randomized trials into clinical care

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In an impressive scientific and organizational feat, researchers, health care workers and patients in the United Kingdom rapidly generated evidence that has transformed the care of patients with coronavirus disease 19 (COVID-19) worldwide. In so doing they have provided an example that Canada should emulate.

On Mar. 19, 2020, a randomized trial called RECOVERY (Randomised Evaluation of COVID-19 Therapy) enrolled its first patient. This UK study was designed to determine, among other things, whether dexamethasone (a readily available, inexpensive medication) is better than usual care without dexamethasone for patients admitted to hospital with COVID-19. Less than 4 months and 6424 patient participants later, the results had been analyzed and released.^{1,2} Dexamethasone significantly improved survival in the subset of patients who were sick enough to require supplemental oxygen or mechanical ventilation.

RECOVERY's results have influenced practice globally because they were convincing. Randomization, which eliminates most confounding, ensured that the improvement seen was due to dexamethasone and not to differences in patient characteristics. Moreover, the primary outcome (death) was unequivocal; enough patients were randomly assigned to make the results credible; study participants appeared similar to most sick patients with COVID-19 (the authors estimated that about 15% of patients admitted to hospital with COVID-19 in the UK were entered into this study³); and the benefits of dexamethasone were substantial (1 patient out of every 8 requiring mechanical ventilation who received treatment with dexamethasone will now survive, whereas without the treatment they would have died). In separate studies, the RECOVERY investigators also convincingly showed that 2 medications used widely in the pandemic's first phase — hydroxychloroquine and lopinavir-ritonavir — are ineffective for admitted patients with COVID-19.^{4,5}

Canada cannot currently match the UK's ability to rapidly conduct such high-priority studies. What can we learn from their success?

The UK has a pre-existing, longitudinally funded clinical research and care improvement network within the National Health Service to conduct research that has passed peer review by the National Institute for Health Research (NIHR).⁶ Centres that participate receive infrastructure support to carry out their work and can, on rare occasions, collectively turn on a dime to focus primarily on 1 project. The UK chief medical officers of health and the NIHR gave

the RECOVERY trial priority status,^{7,8} and 176 academic and nonacademic hospital organizations in the UK participated in the study.² This remarkable institution participation rate maximized the likelihood that the trial results would be generalizable and it indicated clinicians felt both that the research question was important and participation in the trial would not unduly complicate patient care. Data collection at local hospital sites was restricted to essential items and supplemented by outcome data obtained from centrally collected administrative data, made available to researchers (with consent and appropriate privacy protections) in close to real time. Other success factors included rapid and centralized national ethics review and the ability of clinicians in the UK to explain to their patients the implications of participating in the trial (in Canada, clinical care and consent to enroll in clinical trials are kept separate).

RECOVERY has shown how large, well-designed and executed clinical trials that have been identified as priorities can be completed in 4 months. This approach is applicable to many important questions in Canadian health care beyond COVID-19. The noncommunicable diseases that place a great burden on patients and the health and social care systems in our country would be much better managed if we embedded high-priority trials into routine clinical care. The Canadian Institutes of Health Research (CIHR) has invested in COVID-19 research⁹ and other trials, but researchers, and willing patients, are hamstrung by a lack of clinical research capacity and real-time pan-Canadian data integrated within routine care.

Those who manage and fund Canada's health care systems need to view high-priority trials as an integral part of clinical care and to provide adequate and stable infrastructure funding, thus avoiding the current time-consuming and expensive process of developing separate data-sharing agreements and contracts with many hospitals and organizations. Collaboration across Canada's provincial and territorial health care systems is more challenging than in the UK's NHS, but with partial federal funding and federal support it should be feasible. A mechanism should be established, likely through the CIHR, to identify clinical trials that are a national priority according to their potential clinical and health system impact and methodological rigour. This will require a national review panel that includes scientists, clinicians, patients and health system managers. Prioritized national clinical trials must be efficient, with simple criteria for enrolment and data collected on only a small number of important outcomes, supported by rapid

access to interprovincially shared routinely collected clinical data (more rapid than the months to a year it currently takes to access administrative data for research in Canada).

Canadian patients with COVID-19 are currently benefiting from the UK's foresight. It will take a major cultural shift in Canada's attitude toward clinical trials, political will, funding and infrastructure for clinical trials like RECOVERY to occur in Canada, but it can be done, and we must up our game.

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