



How can we increase participation in pandemic research in Canada?

Jennifer L. Y. Tsang, MD, PhD · Robert Fowler, MD, MSc · Deborah J. Cook, MD, MSc · Huiting Ma, MSc · Alexandra Binnie, MD, DPhil

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The COVID-19 pandemic has uncovered long-standing deficiencies in Canada's clinical research infrastructure. Although many Canadian hospitals are participating in COVID-19-related research, the majority of Canadians are cared for in centres where clinical trials are not conducted and therefore have no access to COVID-19 research studies. As a result, recruitment to pandemic trials in Canada has been slow relative to other developed countries

and the proportion of Canadian COVID-19 patients enrolled in clinical trials has been relatively low.

Recognizing the need to expand pandemic research to a broader network of Canadian hospitals, organizations including the Canadian Community Intensive Care Unit Research Network (CCIRNet) and the Canadian Critical Care Trials Group (CCCTG), as well as many individual investigators, have reached out to community hospital clinicians to encourage participation in COVID-19 studies. Nevertheless, infrastructure barriers, such as the lack of pre-existing research programs, research coordinators, research ethics boards, and research policies and procedures, have made participation in these studies challenging or impossible for many hospitals.

Clinical research provides patients with access to novel therapies that are potentially beneficial. Expanding research to a broader network of Canadian hospitals, including community hospitals, would provide opportunities to patients from outside the catchment areas of traditional academic health centres to participate in clinical research, thus improving equity in access to these therapies through clinical research. Health system and health research funding reforms are required to mobilize and support studies across the entire healthcare system, thereby improving research efficiency and ensuring equitable access to clinical research in Canada.

J. L. Y. Tsang, MD, PhD (✉)
Niagara Health, St. Catharines, ON, Canada
e-mail: jennifer.tsang@mail.utoronto.ca

Department of Medicine, McMaster University, Hamilton, ON, Canada

R. Fowler, MD, MSc
Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Department of Medicine, University of Toronto, Toronto, ON, Canada

D. J. Cook, MD, MSc
Department of Medicine, McMaster University, Hamilton, ON, Canada

St. Joseph's Health Care, Hamilton, ON, Canada

H. Ma, MSc
MAP Centre for Urban Health Solutions, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

A. Binnie, MD, DPhil
Willam Osler Health System, Brampton, ON, Canada

Algarve Biomedical Centre, Faro, Portugal

How is clinical research conducted and funded in Canada?

In Canada, although variably labelled and defined, hospitals are broadly divided into “academic” and “community”. Academic hospitals, particularly those that are fully affiliated with universities, view research as one of their core mandates. Academic hospitals account for approximately one-third of total hospital beds in Canada but are the main drivers of health research. Community

hospitals account for the remaining two-thirds of hospital beds in Canada and are focused primarily on health services delivery. During the COVID-19 pandemic, community hospitals have assumed the majority of COVID-19 patient care. Ontario Ministry of Health data reveal that community hospitals accounted for 75% of COVID-19 patient hospital-days in Ontario as of 12 January 2021.^{1,2} While some community hospitals have partial university affiliation and may participate in research, relatively few have a significant research footprint. There is no obligation on the part of Canadian hospitals to participate in research and, in general, few facilitators or institutional incentives exist.

Differences in how health services and health research funding are distributed also contribute to the discrepancy between clinical care and research. In Canada, health services funding is distributed regionally through provincial/territorial Ministries of Health (with federal funding for certain components of territorial healthcare), while health research funding is distributed at the national level chiefly through the Canadian Institutes of Health Research (CIHR). This separation of funding for health services and health research leads to a lack of coordination between the two endeavours and a failure to integrate research into routine clinical practice.

Finally, funding to support clinical trial participation is geared towards hospitals with pre-existing research infrastructure. Typically, hospitals receive a fixed amount of “start-up” funding for a study, followed by a “per-patient” payment for each patient enrolled. Start-up funding is calculated to support hospitals that are research-ready, with all of the necessary infrastructure and personnel in place. Similarly, per-patient payments are based on the assumption that experienced research coordinators are available to screen, recruit, and collect patient data. This funding model does not take into account the time or human resources required to build a research program from the ground up. Moreover, there are few external funding mechanisms to support hospitals that are interested in establishing new research infrastructure.

As a result of these challenges, and despite the eagerness of many frontline clinicians to participate in research on COVID-19, only a handful of Canadian community hospitals have engaged in pandemic studies.

What is the current pandemic research landscape in Canadian hospitals?

One of the largest COVID-19 studies in Canada is the Canadian branch of the World Health Organization’s SOLIDARITY Trial—Canadian Treatments for COVID-19 (CATCO). As of 25 January 2021, only 67 out of 628

Canadian hospitals³ were participating in CATCO, of which 20 were community hospitals. From March 2020 to January 25, 2021, a total of 1,144 patients were enrolled in CATCO, representing 3% of hospitalized patients with COVID-19.⁴ Community hospitals contributed to only 28% of these enrolments (Table 1). Similarly, the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial, a flagship intensive care COVID-19 study, has recruited in 28 of 286 adult intensive care units (ICU) in Canada,³ of which seven were in community hospitals. As of 25 January 2021, REMAP-CAP had enrolled 294 patients in Canada, representing 4% of COVID-19 patients cared for in Canadian ICUs.⁴ Of these 294 patients, only 64 (22%) were enrolled in community hospitals (Table 1).

Although the proportion of patients from community hospitals in CATCO and REMAP-CAP is low, these two trials may have better representation from community hospitals than other in-patient trials, for which community hospital research engagement is typically even lower.⁵

These recruitment numbers contrast with the high level of interest in pandemic research among members of the public as well as among many community physicians. During the first wave of the COVID-19 pandemic in Canada, we conducted a cross-sectional online survey of Canadian community ICU stakeholders including physicians, allied health professionals, research staff, and hospital administrators to explore ICU characteristics, ICU research infrastructure, motivating factors, perceived facilitators, and perceived barriers of pandemic research participation. The survey was disseminated through CCCTG, CCIRNet, Canadian Critical Care Society, and social media platforms. The majority of the 18 participating ICUs were in Ontario, followed by Alberta and Manitoba. Among physician respondents, 88% were interested in participating in pandemic studies but only 40% were doing so. Motivating factors included the desire to improve clinical care and patient outcomes and to advance medical knowledge. Research infrastructure varied widely among the 18 community hospitals (Table 2). The most common perceived barriers to research were lack of start-up funds for a research coordinator and inadequate per-patient reimbursements to sustain an ICU research program. In summary, the survey illustrated a significant mismatch between the enthusiasm of clinicians to participate in pandemic research and the likelihood that they can do so, with lack of financing and research infrastructure being key barriers.

Table 1 Patient enrolment data (as of 25 January 2021) of treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO) and Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)

	CATCO	REMAP-CAP
Total hospitalized COVID-19 cases in Canada	39,171	39,171
Total ICU COVID-19 cases in Canada	7,089	7,089
Total enrolment in Canada	1,144	264
Enrolment from academic centres in Canada	813	200
Enrolment from community centres in Canada	331	64
Total global enrolment	~15,000	5,058
Number of participating academic centres	47	21
Number of participating community centres	21	7

ICU = intensive care unit

Table 2 Pre-existing research infrastructure in a survey of 18 community hospitals in Canada.

Pre-existing research infrastructure	Number of community hospitals	Proportion of community hospitals surveyed
Pre-existing research program(s) in hospital	10	56%
Research policies and procedures	10	56%
Local research ethics board	9	50%
Pharmacy department with research capability or experience	9	50%
Hospital research administration/office	7	39%
Research coordinator(s) or research assistants(s) in hospital	6	33%
Remote research ethics board	4	22%
On-site contract review capability	4	22%
Clinical laboratory department with research capability or experience	2	11%
Diagnostic imaging department with research capability or experience	2	11%

How does health research in other countries differ from Canada?

In the UK, a coordinated health research system has ensured a strong contribution to studies that have informed the treatment of COVID-19. Unlike Canada, the health service sector in the UK intersects closely with the health research sector through the National Institute for Health Research (NIHR).⁶ The NIHR was designed to provide the National Health Service with research support and to coordinate the efforts of networks, National Health Service trusts, and universities. The NIHR, through its Clinical Research Network (CRN),⁷ provides funding that supports research infrastructure at individual hospital sites. The CRN comprises 15 local clinical research networks and 30 specialties that coordinate and support the delivery of high-quality research by geography and clinical area. It provides funding for staff, facilities, equipment, and support services for research. It also provides specialist training,

information systems to manage and report research, and patient and public engagement initiatives.

The NIHR has had unparalleled success in engaging UK hospitals in pandemic studies. In March 2020, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial was chosen by the UK Department of Health and Social Care as an urgent public health study, receiving full funding support from the NIHR CRN. In just 100 days, RECOVERY enrolled over 11,000 patients at 176 hospitals across the UK and was the first study to identify the benefit of corticosteroids in the treatment of hospitalized COVID-19 patients. RECOVERY was also the first study to confirm that treatment with hydroxychloroquine and lopinavir/ritonavir has no benefits.⁸⁻¹⁰ The results of the RECOVERY trial were so convincing that worldwide practice changed almost immediately. As of 4 February, 2021, over 35,000 UK patients had been enrolled in RECOVERY,¹¹ representing 10% of COVID-19 hospitalized patients in the UK.¹² This

is a striking testimony to the power of integrating health research and healthcare delivery.

Although the UK has perhaps the world's most developed national clinical research network, Australia and New Zealand also have a research infrastructure that enables rapid response to clinical needs. The Australia and New Zealand Intensive Care Society (ANZICS)-Clinical Trials Group—modelled on the Canadian Critical Care Trials Group—supports clinical studies across its 74 adult and pediatric ICUs, in part by providing financial support for research coordinators to enable ICUs to start research programs. The Australian Partnership for Preparedness Research on Infectious Diseases Emergencies (APPRISE) has also been funded by the Australian government specifically to build pandemic research preparedness.¹³

The European Union (EU) is currently building a network of over 600 primary care sites and 600 hospital sites across 27 EU member states to conduct large-scale clinical research studies on emerging infectious diseases called the Platform for European Preparedness Against (Re)emerging Epidemics (PREPARE).¹⁴ It establishes a common European clinical research infrastructure to ensure that clinical trial capacity is available to respond to future infectious disease epidemics.

How can we improve Canada's clinical research infrastructure?

To fundamentally improve Canada's research system, we must expand clinical research to more hospitals across Canada, including large suburban community hospitals and smaller rural and northern hospitals. Achieving this goal will require a change in the organization, financing and culture of health research.

Culture change requires both grassroots and top-down approaches. Grassroots movements, such as CCIRNet, can help engage and support frontline clinicians and research personnel to participate in research. Nevertheless, there must also be recognition from federal, provincial and territorial governments of the central role research plays in a learning healthcare system. Government support is mandatory to build and maintain a research infrastructure that can inform best care—to prove which medications and interventions work, and to show which do not work or cause harm. This type of pragmatic, patient-centred research can ultimately reduce health system costs.¹⁵

Funding support for such a learning health system research is a necessity. Research infrastructure investment includes support for research ethics boards, contract review, research coordinators, establishment of research policies and standard operating procedures, longitudinally maintained databases, as well as research pharmacy and

laboratory services. These costs are not typically supported by provincial or territorial hospital budgets. Moreover, research funding agencies, such as the CIHR, do not provide funds to develop and maintain longitudinal research infrastructure through the ebb and flow of studies. The recently announced CIHR Network of COVID-19 Clinical Trials Networks¹⁶ is an important step in this direction. Canada would benefit from a restructuring of the research funding framework, such as that in the UK with the creation of the NIHR, to provide dedicated research funding to hospitals. Such core research infrastructure funding would be in addition to individual study funding and would insure the long-term sustainability of these programs. Productivity could be incentivized through study-specific per-patient payments (similar to the current system) coupled with performance-based biannual infrastructure investment.

Ideally, research should be considered a core activity for all hospitals, including community hospitals—a concept that could be reinforced by making research an accreditation standard through Accreditation Canada,¹⁷ indexed to hospital size and resources. Coupled with the “carrot” of targeted research financing, a research accreditation standard could serve as a significant additional incentive to establish and grow research programs. Hospitals would be free to choose their areas of research interest, in accordance with their clinical needs and the needs of their local community.

Canada's academic hospitals need to be engaged in this remodelling, creating a hub-and-spoke organizational design that connects academic centres with neighbouring community hospitals, similar to the Canadian Cancer Clinical Trial Network (3CTN.ca). Academic centres can help vet clinical trials, provide ethics expertise, and train research coordinators, pharmacy and laboratory staff in research best practices. A clinical trial management system to centralize and track clinical trial activities, staffing, milestones, metrics and finances, such as in the case of the 3CTN, could also offer expertise, improve site performance and enhance collaborations.

Finally, Canada must better integrate healthcare delivery with health research. This would not only improve research efficiency but also accelerate knowledge translation. A research regulatory body, similar to the NIHR in the UK, that can set national research priorities and ensure that research and clinical priorities are aligned, is required. The coordination between major funders, such as the CIHR and the National Science and Engineering Research Council, and provincial and territorial health systems will be crucial for a truly integrated health system that combines healthcare delivery and health research.

Conclusion

Canada is lagging behind other countries in clinical research because the research funding system is detached from clinical care. This is exacerbated by the limited research engagement of hospitals where most patients receive their care. Solutions are at hand. Canada has enormous untapped potential to contribute to medical innovation and knowledge translation that will improve the health of Canadians and improve our healthcare system. The scientific community, research funding agencies, healthcare regulatory bodies and governmental agencies must work together to overhaul the existing research system in Canada and create a truly national research infrastructure. With a new vision, and harmonized efforts from relevant stakeholders and beneficiaries, Canada has the potential to create a true learning healthcare system that innovates and discovers best practices in all hospitals where Canadian patients are treated.

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