

The challenges facing Canadian trialists in an increasingly competitive global market: What can be done to remain competitive?

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Globally, the pharmaceutical industry is condensing into fewer, larger international corporations. This has occurred with the vaccine industry in Canada, where two domestic producers have been absorbed by international companies. This changes the relationship between Canadian vaccine researchers and corporate head office research directors, who carefully assign prelicensure studies to potential market countries around the globe. To succeed in attracting prelicensure vaccine studies, Canadian researchers need to be outstanding in quality, reliability and efficiency. The present article highlights strategies to help researchers remain internationally competitive for industry-sponsored pharmaceutical studies.

Key Words: *Global; Immunization; Research; Vaccines*

Life for clinical trialists in Canada is becoming increasingly challenging, whether trials involve drugs or vaccines. The purpose of the present review was to examine the changing international market for clinical vaccine trials and how Canadian trialists must adapt to remain competitive. A vaccine research perspective may not be wholly applicable to drug evaluations, but many similarities exist.

The vaccine industry is the 'poor cousin' of the pharmaceutical industry, with annual global sales totalling approximately US\$2 billion. That amount is often exceeded by the annual sales of just one blockbuster drug. Vaccines offer limited profits because they are expensive to bring to market (typically costing US\$80 million to US\$100 million) and, by nature, are administered only once or a few times per individual. Moreover, vaccination programs in Canada are government-funded and provinces use their bulk purchasing powers to keep prices low. The fact that vaccines do enormous good for the human race is a relevant motivator, giving credit to companies beyond the relatively limited return on investment.

Vaccine trials are typically of short duration, involving observation of safety and immune responses following a particular immunization regimen. Participants are usually healthy, altering the recruitment task compared with drug evaluations in ill persons. Most vaccine trials in Canada involve phase 2 (preapproval) or phase 4 (postapproval) studies. The regulatory

Les défis qu'affrontent les concepteurs d'essais canadiens dans un marché mondial de plus en plus concurrentiel : Que faire pour demeurer concurrentiel ?

Sur la scène mondiale, l'industrie pharmaceutique fusionne en corporations internationales plus vastes et moins nombreuses. C'est ce qu'on observe dans l'industrie du vaccin au Canada, où deux producteurs nationaux ont été absorbés par des sociétés internationales. Cette situation modifie la relation entre les chercheurs canadiens sur les vaccins et les directeurs de recherche des sièges sociaux de sociétés, qui attribuent consciencieusement les études avant homologation à des pays qui constituent des marchés potentiels autour du monde. Pour réussir à obtenir des études avant homologation sur les vaccins, les chercheurs canadiens doivent être exceptionnels du point de vue de la qualité, de la fiabilité et de l'efficacité. Le présent article expose des stratégies pour aider les chercheurs à demeurer concurrentiels sur la scène internationale afin d'obtenir des études pharmaceutiques subventionnées par l'industrie.

agency is the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada, which is separate from the Drugs Directorate. The same code of good clinical practices applies to vaccine and drug trials.

The vaccine trial community in Canada is small, but remarkably collaborative. Most researchers in academic and public health settings belong to the Canadian Association for Immunization Research and Evaluation (CAIRE <www.caire.ca>), a nonprofit collaboration and research advocacy initiative. Several multi-investigator groups conduct vaccine-related studies continuously, while some smaller teams do so intermittently. Several small and large contract research organizations (CROs) also engage in vaccine research to varying degrees. Larger CROs are used by vaccine manufacturers with limited research supervisory capacity in Canada, while smaller CROs are favoured for trials conducted mainly for regulatory purposes, with limited publication potential.

A fundamental paradox exists for academics involved in sponsored research. Companies expect a business-like relationship with study contractors, but this can be an awkward role for academic and public health researchers confronted with the inevitable contradictions in wishing to be involved in interesting projects while breaking even or turning a small profit. This places researchers at risk of underestimating their budget requirements and incurring a deficit, the effect of

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TABLE 1
Common challenges for Canadian trialists and potential remedies

Challenge	Remedy
Canada is a small market for routine vaccines (approximately 1% of global sales): no sales and no research investment	Federal-provincial purchasing policies that give competing products shared access to the market
Canadian wage rates for research staff are relatively high	Qualified, well-trained, resourceful staff, efficiently used, offer good value
Data from preclicensure trials must support licensure applications in many countries	Canadian study sites should meet the research standards of all major regulatory agencies (the FDA, the EMEA and the BGTD)
Increasing involvement of Canadian centres in multinational trials, requiring coordinated start times	Canadian centres should press for efficient, local study approval processes (ethics and contracts)
Studies in Canada usually require multiple participating centres	Researchers should develop networks of skilled sites that are able to work well together
Newer vaccines target a wide range of age groups	Centres must have efficient means to recruit subjects of all ages, from infants to seniors
Retaining research personnel between studies to avoid loss of expertise	A good business model can help to ensure that centre staff are kept busy with a wide range of projects, with various sponsors
Centres that require continuous project funding to survive are fragile	Infrastructure awards to centres increase their stability and competitiveness, as other countries have demonstrated. Canadian initiatives need to be expanded

BGTD Biologics and Genetic Therapies Directorate; EMEA European Agency for the Evaluation of Medicinal Products; FDA Food and Drug Administration

which can be the extinction of a research team. As a group, clinical researchers are not well prepared to cope with aggressive business practices by sponsors. By virtue of interacting with the industry, researchers may be considered ineligible to serve on immunization advisory committees, confounding the efficient translation of research insight.

Challenges for Canadian vaccine researchers

Canadian vaccine trialists face numerous challenges (Table 1), starting with the reality that the BGTD has no minimum 'Canadian content' rule for products being considered for licensure. New vaccines can be licensed without prior studies in Canada if the regulators believe that the data generated elsewhere (such as in the United States [US]) will apply domestically. Although investigators may be sought out for their expertise with a particular disease, they may only enjoy favour for a brief time, because the trial cycle for specific vaccines is usually complete within a few years. Canadian academic and public health groups mainly depend on continuous project activity to maintain their staff payroll, for lack of any core infrastructure support. This contrasts with the situation in the US, where the National Institutes of Health funds a network of six vaccine evaluation units. Dependence on project-to-project funding permits little unfunded collateral staff activity such as staff development, refinement of standard

procedures or innovation in general. Grant-funded projects can fill activity gaps, but often result in a net financial loss given limited application success rates, incomplete budget awards and incomplete recovery of planning phase costs.

The biggest challenge for vaccine trials is the recruitment of volunteers. Subjects must usually be healthy, requiring recruitment efforts directed more toward the community than health facilities. Current privacy laws severely limit options to canvass the public using administrative databases. Researchers must find the means to recruit age groups from infants to seniors because recently available vaccines target the full age spectrum. While adolescent and adult volunteers may find financial incentives attractive, research ethics boards generally limit payments to necessary expenses, such as parking fees. Factoring these and other considerations together, it is not surprising that approximately only 5% of people who are approached for a given vaccine study actually agree to participate.

Newest challenge: The shrinking vaccine industry

The fact that Canada has lost its independent, domestic vaccine manufacturers (such as Connaught Laboratories [Toronto, Ontario] and ID Biomedical Corporation [Burnaby, British Columbia]) to take-overs by large international companies means that the favoured relationship that once existed between 'local' companies and researchers has ended. Globally, the vaccine industry has condensed to five main companies: Novartis Vaccines (USA), sanofi-aventis (France), Wyeth Pharmaceuticals (USA), Merck Inc (USA) and GlaxoSmithKline (Belgium). These companies develop a comprehensive product evaluation plan for each new vaccine, including consideration of which countries will be selected for specific trials. The priorities that research directors consider in making such project allocations include: which countries offer greatest future sales of the product; which countries can conduct trials most economically; how to ensure adherence to the product development schedule, especially for first-to-market products; and how to simultaneously meet requirements of multiple regulatory agencies. Research directors must also juggle demands for studies from their many affiliates around the globe, some of which are more capable of organizing studies than others.

How well does Canada fare by such criteria? On the negative side, our market potential represents only approximately 1% of global vaccine sales, and our study costs are relatively high because of high wage rates for personnel. On the positive side, qualified, reliable, proficient research teams are available, and most Canadian subsidiaries have project management capabilities, particularly those with research and manufacturing facilities in Canada. However, not all trial protocols are feasible, because of international differences in schedules and existing programs.

Canadian trialists face increasing competition from trial centres in central and eastern Europe and in Asia. These centres have a number of potential advantages, starting with low labour costs for study personnel. Large populations, centralized health care systems and less concern about personal privacy facilitate recruitment. Subjects are usually highly motivated to enrol, because the vaccine offered typically represents a real benefit not otherwise available or affordable. Investigators are typically well motivated too, because payment for their services is a welcome supplement to otherwise low professional incomes. Investigators in central and eastern Europe benefit from the openness of the European Medicines Evaluation

Authority to data generated in any European Union member country, provided that the data are of suitable quality.

Several other trends are of concern for Canadian trialists. Provincial measures to control spiraling drug budgets by preferring generic drugs and limiting the use of patent-protected medications will potentially reduce research investment by the major companies, including the sponsorship of vaccine trials. Companies are increasingly distributing individual studies among multiple countries, as a political and registration expedient, thereby ensuring that some experience with the product has been generated in many countries with marketing potential. For individual trial centres in Canada, this often means small quotas and/or competitive enrolment, with international 'benchmarks' used to determine budgets rather than actual local costs. Small quotas for enrolment are problematic because they preclude economies of scale and exaggerate local costs, because study development and planning costs (typically approximately 25% of overall study budgets) must be amortized over relatively few subjects. Worse still is competitive enrolment without a guaranteed minimum, without which planning costs may not be recovered. The CAIRE investigators have been pressing for either guaranteed minimum enrolment quotas or separate planning phase budgets, but even with such protection, the profitability of sponsored trials is becoming increasingly marginal, placing centres in growing financial jeopardy. Without some profit to maintain payrolls between studies, centres will not be able to sustain themselves.

Company officials point to several systemic problems that make Canadian studies less attractive. They complain that universities take too long to approve clinical trial agreements, with costly involvement of lawyers on both sides. Developing standard trial agreement templates and language would potentially improve the situation. The same complaint is made about the ethics approval process, which can take months when hospitals, universities and, sometimes, provincial committees are involved. This can hamper the start of multi-centre trials and jeopardize individual centres in competitive enrolment situations. A harmonized review process is needed, with more attention paid to the realities of sponsored research.

SURVIVAL STRATEGIES FOR CANADIAN TRIALISTS

The CAIRE executive members have identified five strategies to ensure the continuing viability of the clinical vaccine research capacity in Canada:

1) Centres should know and meet the research standards of the major regulatory agencies (the BGTD, the Food and Drug Administration, and the European Agency for the Evaluation of Medicinal Products)

This ensures that sponsored studies performed in Canada will support licensure applications globally. However, meeting these standards requires time and effort for the research teams. Institutions should help their trial constituencies by offering templates for an appropriately broad range of standard operating practices and training programs for investigators and staff.

2) Centres should press for efficient local study approval processes

To compete effectively in this newly globalized industry, centres must be able to initiate studies in a moderately rapid

and predictable fashion. The use of standard contracts and harmonized ethics reviews would help considerably. Research ethics boards typically charge substantial fees to consider an industry-sponsored trial, but they do nothing differently to expedite the review process. More attention should be given to accommodating competitive situations. A coordinated institutional effort should be directed at changing provincial privacy legislation to allow sharing of health data for research purposes, so that individuals can more readily hear about research participation opportunities from researchers themselves.

3) Researchers should develop networks of skilled trial sites that are able to work well together

This has been a priority of CAIRE for vaccine trials and offers many practical advantages. Investigators at the various centres involved in planning a new trial can reduce their costs by sharing key tasks among themselves rather than duplicating them. Examples include budget formulation, polishing the consent form and negotiating changes in the draft protocol to work optimally in Canada. Networks can potentially share various resources, such as immunoassays. Across the CAIRE network, investigators have established a substantial repertoire of advanced immunoassays that can be used in support of grant-funded projects or to add value to industry-funded projects. Data management capabilities can be shared when needed for grant-funded projects or those funded by smaller biotechnology companies. The latter are increasingly prominent in vaccine discovery research and will benefit from collaborations with skilled trials groups to complete phase 1 'proof of principle' clinical studies. Collectively, investigators are better able to organize training for coordinators, junior investigators and others. Successful, efficient functioning of such networks will help to build an international reputation for Canadian trialists, ensuring their ongoing attractiveness to large, international companies. Within Canada, such networks can potentially work with sponsors to improve the climate for research, as the CAIRE has done with vaccine manufacturers, to address a range of concerns.

4) Centres should adopt a good business model

The successful Canadian vaccine research groups have used variations of the same model, which involves multiple researchers using the same field team and pursuing a wide range of activities, so as to access many funding sources. Collaborators ideally have a range of complementary backgrounds, such as pediatrics, internal medicine, public health, immunology and epidemiology, to provide the breadth needed to study vaccines across the full age spectrum, from infants to seniors, and the full range of issues (disease burden, trials, post-marketing studies and program support studies). A broad skill set allows groups to be active within each stage of vaccine development and to move ahead from one new vaccine to the next. With many options for funding, groups can more readily keep continuously busy and avoid debilitating staff lay-offs. Centres should actively network with skilled peers, with a willingness to share resources. While the 'business' of groups in academics and public health is to conduct good quality research rather than generate profit, the overhead (indirect costs) paid to their institutions by study sponsors is not trivial and should be directed, in part, at improving local research support processes.

5) Change the paradigm!

While each of the aforementioned strategies has merit, the reality remains that vaccine centres that must 'work to survive' are fragile entities. A single major set-back could extinguish a group or centre. Fortunately, governments are beginning to realize that it is in the national interest to ensure that clinical research surge capacity exists in emergency situations, such as an influenza pandemic. There is growing willingness to subsidize vaccine research infrastructure, through development of specialized facilities (Canada Foundation for Innovation), research chairs in vaccinology (Canadian Institutes of Health Research), core personnel funding programs (Michael Smith Foundation for Health Research in British Columbia) and others. Long-term projects, such as the Immunization Monitoring Program ACTive surveillance network among Canadian pediatric centres, provide some stability. In the US, funded networks exist for vaccine trials, preventable disease surveillance and vaccine safety. In Canada, the possibility exists that a network including several trial centres will be developed within the Pandemic Influenza Preparedness program. These developments can change the paradigm favourably to 'work to survive, with some security', because they will not replace projects as the main source of personnel funding. However, even modest discretionary funding can secure the positions of key personnel and enable them to devote more time to developing the centre (standard operating procedures, training and problem solving) and pursuing innovations to increase capabilities and competitiveness. A

particular advantage of having some core funding is that it removes the disincentive that otherwise applies to grant-funded research, at a time when an increasing number of such opportunities are being made available.

SUMMARY

The 'globalization' of the vaccine industry requires Canadian researchers to adapt by becoming more competitive for fewer sponsored projects with tighter budgets. A suitable business model for the evolving situation places emphasis on a broad scope of activities achieved through multi-investigator and cross-disciplinary collaboration locally and nationally. External funding assistance will enhance both the durability and competitiveness of centres. Linking centres within identifiable, specialized networks favours international competitiveness, as well as readiness to respond to national threats and opportunities. Networks give identity to research communities, facilitating dialogue with governments about national expertise requirements and with the industry about improving sponsored research.

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