CSCI/RCPSC HENRY FRIESEN LECTURE

Clinical research in Canada: the dawn of a new era?

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Abstract

In response to the growing gap between discovery and the optimal application of medical advancements to health care delivery, countries the world over have developed large and well funded programs to reduce these gaps. Although these programs vary in nature, they have generally largely focused more on reducing the gap in bench to bedside research. Canada's strong biomedical and patient oriented research (POR) community has a strong base from which to build, but requires support in order to fill the missing elements needed to take full advantage of the important unmet needs in health related research. In Canada, a coalition of funders of medical research, led by the Canadian Institutes for Health Research (CIHR) is developing a large and comprehensive program to build a Canadian infrastructure that will provide these missing elements, and further strengthen POR in Canada. This coalition proposes to put particular emphasis on bedside to community POR, including phase 3 clinical trials, to take advantage of and improve the sustainability of Canada's unique universal health care system. The major initiatives in POR developed by so many countries, including Canada clearly heralds a new era in clinical research, one that the Canadian research community needs to take full advantage of.

Definitions

For the purposes of this paper, the definition of patient-oriented research (POR) is based on that of the NIH: research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator

directly interacts with human subjects. Knowledge translation 1 (T1) refers to knowledge required for going from discovery to the bedside, and provides the knowledge required to understand the rationale for, to develop, and to evaluate the therapies of today and tomorrow (Figure 1).¹ Knowledge translation 2 (T2) refers to knowledge required for going from the bedside to the community, and provides the knowledge required to: evaluate how to best apply knowledge to clinical practice; how to best evaluate clinical issues (epidemiology); how to modify health systems; how to best address public health and population issues. T2 assures optimal utilisation of clinical knowledge and the huge resources applied to assuring the good health of a population.

A call to action

Although the number of papers in POR has increased slightly faster than the number of papers in health in the last 12 years (47% of health papers in 1996 vs. 51% in 2007), there is growing concern regarding the growing gap between discovery of new therapeutic agents or interventions and their widespread and judicious application in clinical practice.²⁻⁴ This gap exists as it relates to both T1 and T2, and, although the importance of various aspects of these gaps may vary from one country to another, this is a global problem

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FIGURE 1. 'Blue Highways' on the NIH Roadmap

that has led to the development of action plans in a large number of countries.

In Canada, the appreciation of the importance of this gap by the Canadian Institutes for Health Research (CIHR) has led it to question whether it was optimally fulfilling its mission: *"To excel, according to internationally accepted standards of scientific excellence, in creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system"*, and to conclude that it was not. As a result, the leadership of the CIHR was asked by Governing Council to develop an action plan for the development of translational and clinical research, and to do it as a cooperative effort with its major partners; the various levels of government (including regional health authorities), industry, charities and foundations, and academic institutions involved in various aspects of health education, research and care.

Canada's present global positioning, the good and the bad

Compared with other leading countries, Canada's proportion of papers in POR has been increasing faster than in most countries over the last 12 years, such that by 2007, its proportion of POR papers had increased to 50% of health related papers in Canada, equivalent to the world average.³ Canadian papers have the highest average relative citations per POR paper in the world, being 42% higher than the world average. Indeed, Canada has the greatest impact of all of the leading countries in POR. These encouraging results, nevertheless, must be viewed in the context of a world-wide deficit in T1 and T2, a problem that is at least as important in Canada than in the rest of the world. Also, in Canada, a relatively small proportion of its peer-reviewed health papers are the published results of clinical trials (6%), and this proportion has been fairly constant in the last 12 years.

FIGURE 2. Distribution of those physicians who reported research by workload category: source 1997 to 2003 CMA Physician Resource Questionnaires; 2004 and 2007 National Physician Surveys (CFPC, CMA, RSPSC)

Some of the problems facing Canadian investigators include:

- 1) Relative underfunding of POR, with approximately 6% (60M\$) of the CIHR budget going to support POR.
- 2) Although small and medium trials addressing clinical practice issues have been funded from Canadian sources, it has been extremely difficult, if not impossible, to fund larger trials answering important clinical issues such as those comparing two strategies and cost effectiveness of care of the same patients. Funding for clinical trials has been lacking, and accounts for only 3% (30M\$) of CIHR funding.
- 3) Support of clinicians to develop and maintain research careers has been lacking, such that the number of clinicians heavily involved in POR has not increased at the speed with which research funding has expanded (Figure 2).⁵⁻⁷ One problem has been our inability to adequately

FIGURE 3. Evolution of women in research (% of total researchers with personal support from Fonds de Recherche en Sante du Quebec 2008-2009-2010)

modify career and research support programs to take into account the realities of the feminization of all health related professions. Women face competing priorities, particularly early in their careers, and, as a result, their scientific productivity frequently suffers and may lead to a change in career path away from research. As a result, the proportion of female clinicians intensively involved in research does not begin to reflect the demographics of health care professionals as a whole (Figure 3)⁸.

- 4) Despite its strength in discovery research, the Canadian research community has a relative weakness in bringing discoveries from their early phases through to market. This weakness stems from the convergence of a number of problems, of which insufficient infrastructure for performing phase 1 and phase 2 clinical trials and insufficient programs or incentives to bring Canadian discoveries forward are but two.
- 5) Although Canadian strengths include world class phase 3 clinical trial centres, as well as world class centres for biomarkers (biochemical, genetic, proteomics, imaging, etc.), with few exceptions, these expertises do not exist in the same centres or, if they do, they frequently do not collaborate optimally to take full advantage of these expertise.

FIGURE 4. Number of new clinical trial applications from 2003-2007 in Canada: Overall clinical trial activities have leveled off, in particular phase II and III, with some increase in phase I activity.

- 6) In Canada, as in other western countries, growing barriers to enrolling patients and to performing trials have led to a shift in performing clinical trials to developing countries.⁹ Other major challenges include high costs, lack of uniform standard operating procedures (SOPs) and contracts, and duration of ethical review process for multisite trials. As a result, investment in clinical research as well as overall investment in research and development in Canada by pharmaceutical industries has not increased over the last five years (Figure 4).¹⁰
- 7) Despite the availability of excellent provincial administrative databases, easy access to these databases is still difficult for much of the research community thereby significantly limiting their research potential and impact on health care.
- 8) Although T2 units exist across Canada, few programs exist to support their ongoing infrastructure which must include people with wide ranging expertises.
- 9) The integration of initiatives from various important funders of research and health care is frequently suboptimal, leading to inefficiencies and under performance. In order to optimally apply knowledge, programs that better integrate the growing expertise of all involved partners, various levels of government, charities, academic units, public health and industry will be required.

The changing global environment

There is a global appreciation of the important gap that exists between biomedical discovery and its application to the understanding, treatment and prevention of human disease. Although programs developed in industrialized countries are addressing aspects of the full spectrum of knowledge transfer (T1 and T2), most developed programs have favoured bridging the gap in T1 in order to strengthen their knowledge based economies.¹¹⁻¹⁴ These programs have focused on creating integrated academic homes for clinical and translational science. They provide the resources to train and advance multi- and interdisciplinary investigators and research teams and to provide them access to innovative research tools and information technologies that apply new knowledge and techniques for patient care. This is usually being done by massive investments in individual institutions with pre-existing strengths. Other programs have had broader goals and have focused more on the general improvement of POR in their country or regionally rather than the development of internationally recognized centers of excellence.¹¹⁻¹⁴

Countries with emerging economies have also realized the need to develop multidisciplinary groups and networks in order to both improve the health care delivery to their patients and to develop their knowledge based economies. China is an excellent example. They have developed a large a number of technologically advanced biomedical research centres, and are developing clinical research networks with the expertise to develop and run all aspects of large clinical trials.

Opportunities for Canada: Guiding principles

Building on our strengths, the need to make choices

The most efficient way of achieving a broad-based improvement of research capacity, is to build around groups that have been successful in competing on a national and international scale, or on strengths and

successful programs specific to Canada. Success breeds success due to good leadership, and is often the result of the convergence of multiple winning conditions that are difficult, if not impossible, to recreate. Indeed, investing in self sufficient teams in order to help them diversify their expertise or to raise their level of international competitiveness is the most productive use of resources and assures the best opportunities for young researchers to benefit from the mentoring required to achieve their full potential. One of the most frequent errors in the development of POR has been the development of infrastructures to support POR with the hope that this would attract and sustain excellence. Although occasionally successful, this well intentioned approach has generally resulted in substantial disappointments and should be avoided.

Any action plan should be built around some of the most important Canadian strengths and initiatives including:

- 1) Our existing centres with strengths in internationally recognized clinical trials development and co-ordination, and our national disease oriented networks.
- 2) Recipients of the national Networks of Centres of Excellence program, recipients of the recent Centres of Excellence in Commercialization, recipients of the FCI-CIHR clinical networks competitions and, in certain cases, the recipients of Canadian Foundation for Innovation (CFI) and the CFI-Hospital awards.
- 3) A strong and diversified biomedical community with centres of excellence in biomarkers and imaging, and other centres with particular well recognized expertises in genomics, proteinomics, bioengineering etc... that can be applied to POR.
- 4) The generally widespread availability of advanced biomedical technology in most Canadian health centres.

- 5) The existence of comprehensive administrative clinical databases associated with our socialized medical system, the strengths and limits of which have been well defined.
- 6) The recent development of schools of public health and strong national and provincial public health units with well developed or rapidly expanding research programs. These, combined with expanding research capacities in regional health authorities and specific provincial units (AETMIS) affords exceptional opportunities to evaluate a whole host important POR questions regarding our health care systems and delivery.

The need for a multidisciplinary approach: the need to partner to meet unmet needs

In addition to building on our strengths, we need to reorganize our resources and invest in the development of groups that not only maximize our forces but also fulfil unmet needs. In the present global environment, where multiple large initiatives are being implemented to favour and support multidisciplinary translational teams, it will be necessary for Canada to favour bringing together groups with various expertises, clinical, biomedical, public health, engineering, etc. Indeed, major initiatives for the development of POR, in this global environment, should require applicants to explain how the complimentary expertises that their team brings together will fulfill an unmet need. The involvement of our strong biomedical community in any application should be viewed as very favourable, as their various expertises will help shape the research of tomorrow. Funding expansion of already successful groups for the extension and expansion of programs that do not propose the integration of significant new biomedical or methodological techniques should generally be avoided unless it continues to meet an unmet need. As few single centres have all of the required expertise to adequately fulfill unmet needs in a meaningful way, as a general rule, collaborative networks (two or more centres or institu-

tions) rather than single centre programs will need to be developed and funded.

The need to partner to adequately fund POR

In order for any program to have a major impact and to compete in this global environment, it will require adequate funding. For this to happen, new money will be required and should be obtained as part of a special initiative funded by the Government of Canada. However, much of the funding will need to come from partnerships between interested groups and from optimization of existing budgets. This reallocation of budgets should come from better targeting of existing funding programs and a shift of resources towards these new initiatives (ex personnel awards attached to the grants of these new initiatives).

The need to target specific infrastructures

In order to build on our strengths, infrastructure programs to promote POR should be focused on developments that permit research teams better access to innovative research tools and information technologies and developments that facilitate the application of new knowledge and techniques to patient care. These infrastructures could be within groups, institutions or networks, and can be regional or national. An example of such a key national infrastructure is a program that would permit the fusion of multiple aspects of provincial administrative databases, which in turn would be accessible to as a large number of Canadian researchers as possible from coast to coast.

The need to increase human resources

Capacity building should be based on the development of a number of strong training milieus which assure excellent mentoring of trainees and young researchers. Training should favour greater integration of inter- and multi-disciplinary research, and favour greater collaboration between institutions. Programs specifically targeting women, particularly during the

early years of their career should be developed and be part of these initiatives.

Opportunities for Canada for bench to bedside and back research (T1)

Although Canada has already many strengths in this area of research, there nevertheless remains many unmet needs in these areas of research that the Canadian research community needs to take advantage of. Also, as stressed above, associating aspects of these fields of research to T2 will serve to strengthen these initiatives, and, there is little doubt that T1 POR will form the cornerstone of most future developments with industry. The major opportunities and unmet needs are:

- 1) *The development of Core Lab Programs and facilities for the identification of therapeutic targets:* In order to do this, a comprehensive program that supports and encourages the development and integration of large technologically advanced core programs and facilities (tissue banking, biomarkers, DNA, proteomics, or imaging) with centres that have access to large well phenotyped patient cohorts will be required. Optimally, these integrated groups would have access to provincial and national health care databases to assure follow up of these patients, or have prolonged follow up of patients outside Canada, as occurs in clinical trials.
- 2) *The development of technologically advanced multi- and inter-disciplinary Phase 2a Clinical Trial Centres focused on knowledge translation:* Phase 2a research has developed in an ad hoc manner the world over and, at this time, no comprehensive centre exists for that type of study. Canadian centres focussing on this unmet need would require a number of characteristics, some of which would be generic to translational research, and others more particular to this specific challenge. Access to a

large number of patients over a wide spectrum of diseases would be essential as would the capacity to identify positive or negative signals via biomarkers, proteinomics, genomics or imaging in order to help make decisions regarding whether to move to market and/or to phase 3 trials. These centres should also have facilities for cell therapy, and expertise in biostatistics and clinical pharmacology. Such centres should also have the capacity to perform specific phase 1 studies and/or phase 2b trials.

- 3) *Development of geographically centred Phase 3 and 4 Clinical Trial co-ordination centres closely aligned with more basic translational research groups:* Centres performing large clinical trials will need to have international networks in order to retain their leadership positions, and will need to closely align themselves with multi- and inter-disciplinary research teams to foster translational research. They should integrate value added expertises such as imaging, biomarkers, proteomics and genomics, to the trials that they lead. They also need to act as a hub and resource for research groups from other institutions and for disease thematic networks. Partnerships with complementary institutions and groups will be part and parcel of the mandate of these groups. These groups should also have the capacity to support population or epidemiological studies, and optimally, should work to develop primary care research networks. The link to primary care networks is particularly important given that chronic diseases are prime targets for such studies and are generally cared for by primary care health professionals. Primary care professionals are also at the centre of new approaches to improving health care and its delivery, for example collaborative approaches to health care, and thus need to be at the centre of any such research initiatives.

- 4) *Development of enabling tools such as a national ethics board, and a prototype contract (or at least principles or a methodology to be followed).*
- 5) *Development of national research education programs aimed at various health care professionals in order to promote good clinical practices.*

Opportunities for Canada in Bedside to Community and Back Research (T2)

This area of research involves studies that examine the relationship between health care systems and patient outcomes, that produce earlier, more accurate diagnoses of breast cancer or stroke; or studies that better define the long-term outcomes and impact on quality of life of a disease itself and its treatments. T2 patient-oriented research also involves clinical trials that compare treatment options such as drugs and other interventions, to find the ones that produce the best outcomes for patients.

The Patient Oriented Research Initiative

This large POR initiative, named **S**upport for **P**eople and **P**atient-**O**riented **R**esearch and **T**rials (SUPPORT) strategy remains in the development stage and will be presented to the Canadian research community and its funders over the next few months for validation and improvement. For these reasons, it is not possible to outline the details of the final form which this initiative will take, but it is possible to outline some of the underlying principles driving it, and the potential challenges ahead.

The objective of the Strategy is to gather the evidence that will allow health professionals to improve health outcomes for Canadians, by offering cost-effective prevention, diagnostic and treatment strategies. The Strategy revolves around POR that focuses on health outcomes in individuals or groups over a 5- to 10-year horizon.

This 10-year strategy, to be implemented in phases, is designed to gather the evidence that will allow health professionals to improve health outcomes for Canadians, by offering cost-effective prevention, diagnostic and treatment strategies. The strategy revolves around POR that focuses on health outcomes in individuals or groups over a 5- to 10-year horizon.

The proposed program is composed of two main elements, 1) a nationwide research infrastructure around an integrated research model called SUPPORT units, and 2) nationwide patient-oriented research networks on overriding themes to strengthen POR in areas of excellence and of high disease burden, including cardiovascular disease, cancer and mental health.

The 15-20 SUPPORT units would consist of health care personnel with biostatistical, data management and methodological skills to help researchers run their projects. The SUPPORT units will be housed in existing health science centres, or other academic institutions, and are expected to provide easily accessible expertise to clinical researchers of their particular region. The SUPPORT units should generally include personnel with specialized expertise, and thus particular strengths in knowledge translation, co-ordination of complex major national and international trials, large observational studies, phase 1 and 2 clinical trials, translational biology, or systematic reviews. The SUPPORT units will also be expected to collaborate with and support the nationwide patient-oriented research networks.

Other major components of the strategy include the training and mentoring of young clinical researchers with varying expertise, the development of nationwide approaches to ethics reviews, unified contracts and templates, and standard operating procedures. The development of primary care research networks is favoured.

The funding for this initiative is expected to come from the various partners, the contribution of each being concentrated on issues of particular interest to them. These include CIHR, which is expected to re-

structure and enhance existing resources affected to POR, and the federal government which, it is anticipated, will contribute additional funds. The provinces, the charities, industry, and other partners such as academic institutions will complete the funding of various aspects of the initiative.

The governance of this POR initiative will be crucial. The CIHR will be the lead agency responsible for implementing this strategy, and an initiative director (champion) working out of offices at the CIHR will direct the strategy. This champion will report to a board of directors chaired by the president of CIHR, and which will include representatives from the various partners in this collaborative project. The reporting structure of the SUPPORT units is still being worked out and may vary according to the specific structure and mandate of the SUPPORT unit or disease-oriented Network.

Some of the strengths of the initiative include:

- 1) Significant improvement of health care delivery to Canadians over a short time frame, and more efficient use of resources. Together, this should improve the health of Canadians and should contribute to reducing the greatest risk to our health care system, that of sustainability.
- 2) A comprehensive approach to improving T2 POR that should permit the development of projects which will be of interest to all potential partners. For example, charities may support research networks in their disease areas of interest, provinces may fund initiatives that evaluate new and potentially better approaches to health care, and industry may support initiatives that help them fulfill their post-marketing surveillance requirements.
- 3) Increased involvement of the academic community in local and national health care delivery, and better integration of the efforts of all partners towards common goals.

- 4) This initiative, by favouring the development of partnerships, capacity building and funding in research focused on pillars 2 to 4 of the CIHR (clinical; health systems and services; and the social, cultural and environmental factors that effect the health of populations), will significantly contribute to redressing the historic imbalance that has existed in funding between these three pillars and biomedical research (pillar 1).
- 3) The governance of the initiative will be crucial. The champion will need to be a recognized leader in this broad area of research, and, preferably should divest themselves from involvement in their own centre in order to avoid perceived conflicts of interest. As noted above, the structuring of programs will need to factor in the needs of the various partners and will require careful negotiations and transparency. Finally, the reporting structure of SUPPORT unit directors and Network directors will need to be flexible and take into account their specific structure and mandate in order to avoid creating situations that would complicate their development and the advancement of national priorities for the program.

Challenges facing the patient oriented research initiative:

- 1) Although one of the strengths of the program is its comprehensive nature, this also provides one of the major challenges to its overall success. If the primary goal is to develop international excellence in POR, the development of a large number of SUPPORT centres and networks, sometimes in areas with little pre-existing expertise, and lack of internationally recognized leadership risks falling short of the goal. Other countries are generally concentrating their investments in centres with proven track records thus providing a further competitive edge to these centres. Strategic decisions need to be made, and focus is required. Perhaps the development of various levels of funding for centres, more for those with strong global impact, and less with those with more modest goals, will help resolve this potential challenge.
- 2) Although one of the strengths of the program is the broad alliance of interested partners, how the interests of the various partners will be moulded together into a coherent and sustainable program will be challenging, as will the need to convince partners to support aspects of the program not immediately of interest to them. The programs, as they develop, will need the input of all partners and will need the flexibility to meet the aspirations of all partners.
- 4) The biomedical community in Canada is strong and needs to be integrated into this initiative. If successfully integrated, it will add a dimension to T2 that is relatively unique to Canada and will serve to improve our competitiveness by leading to unique and important new discoveries and health care strategies.
- 5) All good initiatives require metrics to better define their goals in order to measure their success and impact. Devising metrics for such a broad initiative will be challenging but essential, and will need to be adapted to the nature of the specific programs developed.

Conclusion

We could, indeed, be at the dawn of a new era for clinical research in Canada. While recognizing the need to further strengthen the translation arm of T1 POR, the leaders of the Canadian patient oriented research and trials initiative propose we concentrate our efforts on health outcomes by significantly investing in supporting and developing T2 POR for a whole host of good reasons. Nevertheless, this initiative should also present excellent opportunities for researchers more traditionally focused on T1 POR to

develop new and unique collaborations with teams performing T2 POR. Indeed, the Canadian research community as a whole must strive to address the unmet needs in both T2 and T1 POR by focussing on optimization of existing programs, by developing multi-disciplinary cutting edge teams, and when possible, by taking advantage of opportunities where aspects of T1 POR can be applied to enrich T2 POR and vice-versa. Although the challenges to POR in Canada remain important, there is little doubt that the Canadian community understands this and is acting proactively to address them.

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