

THE STUDY OF DRUGS FOR RARE DISORDERS: HARNESSING RESEARCH CONTRIBUTIONS BY CANADIAN ACADEMIC INSTITUTIONS

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BACKGROUND

Genetic research in Canadian universities is in the midst of a revolution brought about by new technologies that have led in the past five years to astonishing increases in DNA sequencing capacity at a reduction of per-nucleotide cost of many thousandfold.¹ These and other developments are producing an improved understanding of the genetic landscape of the cell,² and increased insight into the interplay of genetic and environmental factors. These are often manifested in epigenetic changes, which can now also be monitored using high-throughput techniques,³ and which regulate physiologic and pharmacologic processes. Continued progress in the academic setting is critical if Canada is to meet its share of research responsibilities and to use this improved scientific understanding to support optimal patient care.

In October 2012, the Canadian Minister of Health announced Health Canada's commitment to the development of an orphan drug policy. Towards that end, active consultation has been initiated concerning a draft orphan drug regulatory framework.⁴ Those discussions demand consideration of the role that should be played by Canada's academic institutions in providing a research and information base essential to the safe and effective introduction of drugs intended for the treatment of rare disorders. There are many parallels in this situation to the research agenda already being pursued in seeking innovative treatments for disorders that occur in special populations, such as neonates, children, pregnant or nursing women, and the frail elderly.⁵⁻⁷

Relevant activities also include the research required for the repurposing of previously licensed medicinal therapies to support marketing for treatment of more widespread conditions.

The focus on essential research that may be undertaken in Canada's universities is sharpened by the continuing discussion led by the Canadian Institutes for Health Research (CIHR) concerning its Strategy for Patient Oriented Research (SPOR).⁸ If universities are to refine their interest in knowledge gaps that disadvantage special populations, they will inevitably be required to address the concerns of Canadians suffering from any of 7,000-8,000 rare disorders, of which half have not yet been fully characterized or designated but nevertheless can be encountered in clinical practice. While many of these disorders are likely to have genetic etiologies, a multidisciplinary investigative effort will be required to fully understand their natural histories as well as develop novel effective therapies.⁹⁻¹⁰

Establishing research and educational priorities around rare disorders is complicated by the fact that Canada has lacked an orphan drug act and has, to date, not defined what is meant by a 'rare' disorder. In the United States an Orphan Drug Act was passed in 1983 and revised in 2012 as the Rare Diseases Act,¹¹⁻¹² identifying conditions affecting less than 200,000 American citizens as rare disorders. Under that definition, 2,800 potential therapeutic products have already received designation from the FDA as 'orphan products' and the number continues to grow. The European Union has settled on a prevalence of less than 1 in 2,000 individuals for its definition of

'rare' and Canada appears likely to follow this lead.¹³

It seems clear that any concerted effort to improve treatment of rare conditions will require a highly integrated program of basic, clinical and population health research that begins with a commitment to discovery of new therapeutic products or the effective repurposing of existing therapies for rare disease. Much of the relevant research is likely to be conducted in academic centres. It is critically important to create an environment in these institutions that will foster relevant clinical investigation conducted in an efficient manner. Because patient populations are small, it is highly likely that multicentre trials will be the norm. These will be greatly facilitated in the future if current Canadian efforts at inter-institutional collaboration including ethics harmonization prove fruitful.¹⁴

Academic centres specialize in knowledge mobilization and it will be important that they direct such efforts to the transfer of knowledge concerning therapies proven clinically effective to the practice domain, where changes in practitioner behaviour have always proven challenging.¹⁵⁻¹⁶

Clinical trials environment in Canada

The environment for conduct of clinical trials is changing rapidly in Canada and in other comparable jurisdictions. Increasingly, academic centres are struggling to find support for a productive clinical trials environment as investment by the pharmaceutical and biotechnology industries in clinical trials in developed countries is shrinking.¹⁴ This renders prospects for rare disease clinical trials, already confronting a number of issues, even more problematic.

Many of the relevant issues have been highlighted in a summit report prepared in 2011 by CIHR, Rx&D and the Association of Canadian Academic Healthcare Organizations.¹⁴ The theme was further addressed in greater detail by the standing Senate Committee on Social Affairs, Science and Technology in its report of November 2012.¹⁷ The Committee recommended that the needs of special populations should be addressed by Canada's health research institutions and that a responsibility to participate in the pursuit of

relevant clinical research evidence be recognized. Further, the Committee encouraged (Recommendation #5) the creation of research networks as part of its goal of promoting the importance of clinical trials and providing guidance to research networks on centralizing research ethics review and creating databases of patients willing to be considered for participation in investigations. The Senate Committee explicitly advised that Health Canada's approval for new medicines should only extend to cover the population in which clinical trials were performed.

Another recommendation (#7) states, "The committee therefore recommends that the Minister of Health directs Health Canada to include the following elements in its orphan drug policy: creation of orphan drug status for drugs in development for specified rare conditions, assistance in the design of clinical trials for investigational orphan drugs, elimination or reduction of user fees charged by Health Canada for review of orphan drug submissions and extension of market exclusivity for orphan drugs." The latter two points echo policy developments that have already taken place in the US and Europe. A subsequent recommendation (#8) proposed that a national framework for coordinating clinical trials be established with a mandate to "promote Canada as a preferred site for clinical trials of orphan drugs"; and, "include a requirement for consultation with stakeholders, including the Canadian Organization for Rare Disorders, to explore ways to improve and maximize patient recruitments to trials."

If Canada is to pursue an enhanced environment for conduct of clinical trials relevant to rare disorders there will be a clear need to address human resource issues in the area of evaluation science.¹⁸ Put bluntly, Canada currently lacks the human resources necessary to mount a comprehensive rare disease clinical research program, particularly in an area where emphasis will need to be placed on alternative and adaptive trial designs. If, as will most likely be necessary, emphasis is shifted from large multicentre randomized controlled trials to small carefully designed adaptive trials, a new body of expertise will be required and academic centres will need to

make a commitment to develop that expertise.¹⁹⁻²⁰ In this context, the Senate Committee recommended (#6):

1) amendment of trial regulations contained in part C division 5 of the food and drug regulations to stipulate that clinical trials must be designed to reflect the same population that can reasonably be expected to consume the drug once approved for sale, and

2) implementation of modifications to Health Canada's drug approval process to stipulate that market approval will only be granted if clinical trial evidence of the product's safety and efficacy includes data on all population groups that can reasonably be expected to consume that drug once approved for sale in Canada.

Drug evaluation science

The evaluation science supporting regulation of therapeutic products is continuously evolving. Our increased understanding of the human genome, and the resulting pathogenic insight, is being translated into a science of pharmacogenomics that will support a rapid shift toward more personalized therapeutics.²¹⁻²² Increasingly, studies will be conducted in patient populations that have been genomically characterized with likely beneficiaries of therapy preemptively identified. The targeting of therapy, to optimize efficacy and to avoid toxicity, will necessitate new research methods²² and the revamping of approaches taken

by regulatory bodies such as the Therapeutic Products Directorate, Marketed Health Products Directorate and the Biologic and Gene Products Directorate within Health Canada.

The key components in a comprehensive clinical investigation program required for the support of regulatory and clinical decision making are outlined in Table 1. Many of the relevant issues raised by the ongoing paradigm shift have been identified in a second report of the Senate Committee on Social Affairs, Science and Technology issued in March 2013.²³ This report focuses on post-approval monitoring of safety and effectiveness for prescription pharmaceuticals in Canada. The Senate Committee applauded the work that has been done in the past three years by the Drug Safety and Effectiveness Network (DSEN), which is housed within CIHR but created as a partnership venture by the federal and provincial governments of Canada.²⁴ DSEN has an important contribution to make to the new clinical investigation environment required for consideration of drugs for treatment of rare disorders. In this area, again, there is potential pressure on human resources and a foreseeable demand for new post-secondary and post-professional educational programs. There are a few academic centres in Canada that have specialized in safety and effectiveness evaluation but the numbers of graduates remain small, and inadequate to meet the heavy demand that lies ahead.¹⁸

TABLE 1 Key components: clinical studies for rare disorders

• systematic analysis of pre-trial study results
• modeling/simulation capability
• design expertise for small clinical trials (alternative and adaptive designs)
• innovative statistical methods/Bayesian and other non frequentist approaches
• pharmacokinetics/pharmacodynamics
• analytic capacity (relevant to biological entities)
• tools for dosing standardization
• clinical toxicology
• data transfer/data management
• risk management/data safety monitoring
• knowledge transfer strategy

There is a growing belief that the system requires a closer alignment of health technology assessment with therapeutic evaluation, including the generation of evidence from clinical investigations. There are at least five areas that require consideration if improved harmonization is to be achieved.

- Evidentiary needs should be better aligned to reflect the expectations of regulators, manufacturers, patients and clinical caregivers.
- Early dialogue should be encouraged, bringing together government decision makers with researchers, clinicians, patient groups (see below) and sponsors of new products from the pharmaceutical and biotechnology industries.
- Wherever possible, the process should be streamlined so that innovative products are submitted for health technology assessment at the same time as entering regulatory review. Emphasis must be placed as much as possible on the social and clinical context in which the new technology will be applied and not only on the safety and efficacy of the product itself.
- Increasing consideration of some form of adaptive licensing (coverage with evidence development) will facilitate the introduction of innovative therapies. The continuing challenge is to align the best possible advice on the design of pre- and post-market evaluations with the demands of patients, families and clinicians for early access to promising treatments.
- In the case of rare disorders it is critically important to engage patients (and families) at an early stage of product development. Careful observation of a condition's natural history will greatly facilitate later determination of safety and efficacy.

Potential academic contributions

In addition to providing a platform for drug discovery and development and for innovative clinical trials for treatments intended for use in management of rare disorders, it will be essential that academic centres expand their capacity in population health.

A study conducted by Health Canada in 2010 highlighted the academic shortfalls in human resource capacity in Canada relative to the evaluation of new therapeutic products.¹⁸ There appears to be a significant shortfall in all domains where such expertise is needed, government, industry, and in academic health science centres. Unfortunately, Canada's academic centres have, to date, not been able to meet the clear need for a complement of highly qualified personnel equipped to handle the evaluation demands of a clinical world in which personalized therapy is becoming increasingly common.²¹⁻²² Some new disciplines such as epigenetics have gone largely unattended from a population health standpoint, although discovery research in this area is the focus of a major recent strategic funding initiative from CIHR.²⁵

The evolving environment has led to identification of essential science supports required as new ground is broken in fields such as therapeutics for orphan disorders.^{6,26} New approaches to health technology assessment must be developed and must encompass the treatment environment and processes as much as the safety and efficacy of the new treatment. As already described, it is imperative that maximum effort be made to mesh health technology assessment activities with other aspects of regulatory science.

Canada is relatively well served by expertise in health economics and outcome evaluation; however, most such expertise has been focused on reimbursement decisions made in the context of widespread conditions affecting large populations of patients. New approaches and new methods will be required if that foundational expertise is to be brought to bear on the new challenges posed by rare disorders and by personalized medicine approaches.

Decision making about reimbursement for drugs for rare disorders is part of a complex system. Dedicated expertise in social and behavioural science will be required if consistent decisions are to be made about the social justice aspects of decision making.²⁷ Again, academic centres must be expected to familiarize themselves with this changing environment and to encourage development of relevant domains of research expertise.

Needed shift in academic research profiles

Academic health centres in Canada have traditionally excelled in discovery research. CIHR commits approximately 70% of its competitive grants and awards funds to investigator-initiated research projects. These funds provide a critical source of support and have enabled outstanding achievements in biomedical research, contributing, among many other things, to elucidation of disease-implicated genetic pathways that allow identification of promising therapeutic targets and further lead to discoveries of entities with therapeutic potential.

The remainder of the CIHR research budget is dedicated toward targeted or strategic research. Under its present strategic plan, CIHR has identified several priority areas for investment, and among these is Personalized Medicine and Health. In addition, CIHR has given great attention in its SPOR initiative to patient oriented research,⁸ which incentivizes academic centres to direct investigational capacity to the study of optimal disease management, including the translation of knowledge garnered through the basic science programs. These priorities create human resource needs to strengthen a collective capacity for the study of new therapeutic entities.

If Canada is to keep pace with the evolution that is occurring around targeted therapeutics for special populations, including

those with rare disorders, there will need to be a concerted effort made to develop expertise in clinical trial design. This falls within the remit of DSEN,²⁴ but to date no single centre of trial design expertise in Canada has been singled out. One of the first activities of DSEN was the creation of a network for observational drug effect studies (CNODES) but the focus of that group has been diffused across the methodologic realm of observational studies and a call for applications for an innovative trial design centre drew no response from the research community. (Peterson RG, personal communication) A higher-profile effort, potentially linked with DSEN but also with SPOR and/or the Personalized Medicine Signature Initiative, might produce a more positive outcome. Such a development is essential if Canada's capacity in therapeutic evaluation is to evolve at a pace rapid enough to meet the demands placed on the system by drug discovery in the era of understanding of the human genome.⁶

There are some excellent examples of Canadian academic initiatives that at least begin to provide a foundation for the type of reformed environment necessary to support a comprehensive program in development of drugs for rare and neglected diseases. A representative sample of recent promising initiatives is shown in Table 2.

TABLE 2 Representative Canadian academic initiatives relevant to therapeutic innovation for rare disorders

Initiative	Objective	Information
Canadian Pharmacogenomics Network for Drug Safety (CPNDS)	The goal of CPNDS is to prevent adverse drug reactions in children and adults by identifying predictive genomic markers for specific ADRs and to incorporate these into genetically tailored therapeutic recommendations. An additional goal is improved understanding of the genomic determinants of therapeutic drug effects.	www.cpnnds.ubc.ca/
Care for Rare	C4R is a pan-Canadian collaboration of clinicians, bioinformaticians, scientists and researchers building on the infrastructure and discoveries of FORGE Canada (Finding of Rare Disease Genes). The goal is to improve clinical care by expanding and improving the diagnosis and treatment of rare diseases.	care4rare.ca/
Centre for Drug Research and Development (CDRD)	CRDD, based at the University of British Columbia, aims to translate commercially promising health research conducted at the university level into new therapies that improve and save lives. Operating as a national not-for-profit centre, CDRD has a mandate to de-risk discoveries from publicly funded research to create viable investment opportunities for the private sector.	www.cdrd.ca/
Centre of Excellence in Personalized Medicine (CEPMED)	Funded by the Montreal Heart Institute and Genome QC, CEPMED is dedicated to promoting the science and practice of personalized medicine through research, commercialization and education. CEPMED participates in public-private partnerships in translational medicine and fosters pharmacogenetics testing in clinical trials.	cepmed.dnadirect.com/grc/patient-site/home.html
Global Neglected Disease Initiative (GNDI)	UBC is providing leadership in the development of an intellectual property initiative that will harness the economic potential of academic therapeutic and preventive innovations while enhancing social benefit by promoting fair and affordable access in developing countries.	ngdi.ubc.ca/
Mother, Infant, Child, Youth Research Network (MICYRN)	The network provides practice-based research teams with an integrated infrastructure underpinned by a coordinating centre and overseen by a common governance structure that removes barriers and fosters national collaboration around conditions affecting pregnant women, infants, children and youth. Such enabling structures are vital to effective clinical research on rare diseases.	www.micyrn.ca/
Quebec Consortium for Drug Discovery	The Consortium's aim is to identify, fund and support joint research projects between the academic and private biopharmaceutical sectors. Projects funded target the development of innovative tools and technologies that accelerate the drug discovery process.	www.cqdm.org/

Networks and Consortia in Knowledge Mobilization (implementation science)

Consideration of the elements brought into play by rapidly growing research activity in the area of rare disorders emphasizes the extent to which networks and consortia will need to form in order to meet resulting pressures. Canada has done exceptionally well in creating infrastructure to support the type of comprehensive scientific effort that will be needed in meeting the demands for better treatment of orphan diseases in the future. For almost three decades now the federal government has supported the development of networks of centres of excellence.²⁸ Furthermore, the Canada Foundation for Innovation (CFI)²⁹ has successfully created a solid infrastructure in most Canadian academic centres and the program for Centres of Excellence for Commercialization and Research (CECR)³⁰ has directly encouraged the translation of discovery science to clinical evaluation and commercialization.

In the orphan disorder field different types of networks are likely to be required and these are beginning to emerge. CIHR's Institute of Genetics hosts the Canadian node of OrphaNet, an information resource on orphan diseases that is targeted toward patients, clinicians, and researchers. OrphaNet operates in 37 countries³¹ and members of the Care4Rare consortium are engaged in providing content for the Canadian site and in vetting its scientific content. Canadian centres also benefit from engagement with the International Rare Diseases Research Consortium (IRDiRC) which brings together over 30 public and private research funders (including CIHR and Genome Canada) who have collectively pledged upwards of USD 1 billion to support rare disease research. IRDiRC's goals are to achieve 200 new therapies for rare diseases, and to have diagnostic tools for most rare disorders by 2020.³² Since 2012, Canadian rare disease researchers have also been able to seek funding for their part of collaborative projects with European labs through the E-Rare 2 initiative,³³ of which CIHR and the Fonds de Recherche Québec - Santé (FRQS) are members.

In addition, the national and provincial genome funders have enabled, in partnership with CIHR and others, funding for a large body of

research relevant to rare disorders. For example, the recently funded Care for Rare program (Care4Rare.ca), which involves CIHR, Genome Canada, the Ontario Genomics Institute, and Pfizer as partners, successfully bridges many of the concerns expressed in this paper and promises to create a multidisciplinary network based in academia well prepared to address a variety of challenges.³⁴ This is a major step in the right direction.

The future: a new collaboration model

Activities within Canada in the area of developing innovative strategies for handling the therapeutic challenges posed by rare diseases have multiplied in the last three years and many of the elements are now in place that would ensure that Canada plays a leading role internationally in this area in the future. The key to future success lies in a collaborative model that will allow capitalization on the major investments in infrastructure that have been made in Canadian academic centres. It is critically important that all of the participating organizations and institutions contribute in accordance with their strengths and that government agencies such as CIHR, DSEN and the Canadian Agency for Drugs and Technology in Health work effectively with the biotechnology and pharmaceutical industries.

Above all, it is necessary that academic institutions better recognize the pivotal contribution they can make to patient oriented research in pursuit of improved health outcomes for special populations such as those with rare disorders. Canadian academic institutions must also continue to strengthen their efforts aimed at creating an environment that will foster partnership with private sector players. The future is most certainly "not what it used to be". (Paul Valery, French critic and poet, 1871-1945)

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