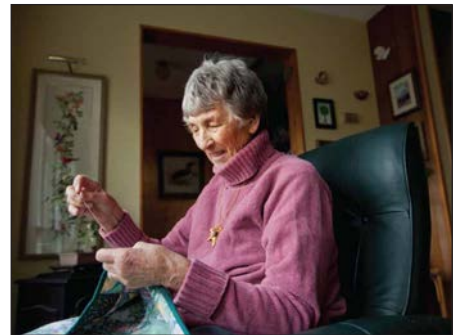
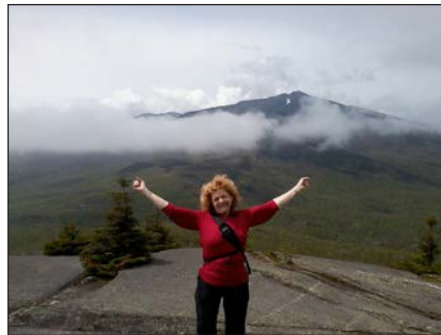




Canadian Organization  
for Rare Disorders

# Now is the Time: A Strategy for Rare Diseases is a Strategy for all Canadians

## CANADA'S RARE DISEASE STRATEGY



### GOALS

1. Improving early detection and prevention
2. Providing timely, equitable and evidence-informed care
3. Enhancing community support
4. Providing sustainable access to promising therapies
5. Promoting innovative research

## *Acknowledgements*

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## Introduction

In Canada, people living with rare disorders face **extraordinary challenges** in obtaining the appropriate health and social care that they need. For instance,

- It took Miriam **six years, 13 specialists, and three misdiagnoses** to get the right diagnosis. In the meantime, she underwent six unnecessary surgeries.
- Tony's **doctors didn't know that the "rare" tumours** that led to his liver failure could have been treated with a readily available cancer drug.
- In Joey's province, **newborn screening did not include his rare disease**. His parents had two more boys with the same condition before they realized something was seriously wrong.

The **burden of rare disorders is significant** and not only impacts as many as 1 in 12 Canadians, but it also affects their families, the healthcare and social systems, the workplace, the economy, and our collective social welfare.

The Canadian Organization for Rare Disorders (CORD) believes that Canada needs a rare disease strategy to facilitate and better coordinate the efforts of governments and stakeholders involved in addressing the current challenges and ensuring that all people with rare disorders across the country can enjoy the same timely and quality health and social care as patients with more common diseases.

Further to extensive stakeholder engagement, CORD has developed, and is calling for the implementation of, Canada's Rare Disease Strategy, which focuses on achieving the **following five key goals**:

1. **Improving early detection and prevention**
2. **Providing timely, equitable and evidence-informed care**
3. **Enhancing community support**
4. **Providing sustainable access to promising therapies**
5. **Promoting innovative research**

For each of these goals, this document highlights the gaps that currently exist and proposes priority actions to help close these gaps. CORD recognizes that Canada already has ongoing initiatives and programs working towards achieving many of these goals. In particular, the Regroupement Québécois des Maladies Orphelines (RQMO) has been developing a strategy on rare disorders for the province of Quebec. The objective of Canada's Rare Disease Strategy is to leverage, build upon and better coordinate Canadian initiatives as well as international programs and collaborations.

**We will be monitoring progress against these goals with all stakeholders. Our shared success will be celebrated when policymakers from all levels of government and the rare disorders community can point to specific initiatives that have improved the lives of Canadians with rare disorders.**

CORD has also developed a set of principles to help guide governments and stakeholders as they move towards achieving the five strategic goals. One of these principles is the need to be **patient-centred**. Specifically, CORD wants to emphasize the need to ensure that all programs or measures related to rare disorders start from the

patients' perspectives and are focused on addressing the needs of patients and their families. Patients and their families must be involved in every step of the process.

Finally, CORD views Canada's Rare Disease Strategy as a living document that will evolve as we move forward in addressing the challenges related to rare disorders, based on dialogue with governments and other stakeholders in Canada and abroad. CORD therefore welcomes any new ideas on how we can, collectively, make a difference to bring real positive change in how we care for people with rare disorders in this country.

### **Context: the Challenge and the Hope for Canadians with Rare Diseases**

At the international level, many countries have formally adopted definitions of the term "rare disease." These definitions vary from one jurisdiction to another. In Canada, the Canadian Institutes of Health Research (CIHR) and Health Canada are developing programs based on the following definition: "*a rare disease is a life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons).*"<sup>1</sup>

It is estimated that there are around 7,000 rare disorders and that they affect 1 in 12 Canadians.<sup>2</sup> The age of onset of more than half of rare diseases is during childhood. Rare diseases include a diversity of disorders. Many are genetic and complex, involving multiple systems in the body. They may be static or degenerative, and are associated with a wide range of symptoms, which vary among individuals with the same disease and may also resemble symptoms associated with more common diseases.

Rare diseases affect a small number of individuals, which means that individual clinical teams may see few to no patients with a given rare disease, resulting in limited and fragmented scientific understanding and clinical expertise. Therefore, individuals are frequently misdiagnosed and/or endure a lengthy diagnostic odyssey until the correct diagnosis is made, delaying access to appropriate care. In addition, many of these diseases do not have effective treatment options, and "appropriate care" is focused on symptom management only. When there are effective available treatments, access can often be very challenging for patients and can vary from one province to another. All of these challenges lead to increased morbidity, loss of life or poorer quality of life and increased costs to the family, the healthcare system and ultimately the Canadian economy.

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<sup>1</sup> See [http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/\\_2012/2012-147a-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2012/2012-147a-eng.php)

<sup>2</sup> <http://raredisorders.ca/aboutUs.html>

## Guiding Principles

**Equity of Access:** Every Canadian with a rare disorder no matter where he/she lives should be provided with the same quality of care and services as other Canadians with more common illnesses.

**Patient-Centred:** Any strategy, measure or program concerning rare diseases needs to start with the patients' perspectives. To ensure that their needs are addressed, patients, and the organizations that represent them, should be involved in every step of the development and implementation of these initiatives. People living with rare diseases have direct experience of how the diseases have affected them and their families and what needs to be done to improve their lives.

**Collaboration and Coordination:** Collaboration among all stakeholders in the rare disease space and coordination of work and efforts are essential given the dispersed and small patient populations and the limited understanding of these diseases. Governments, patients, healthcare professionals, researchers and the life sciences industry must work together at the national and international level to exchange information, experiences and expertise.

## Summary: Goals for Canada’s Rare Disease Strategy

To achieve the five goals of Canada’s Rare Disease Strategy, CORD recommends the following actions:

<p><b>Goal #1: Improving early detection and prevention</b></p> <ol style="list-style-type: none"> <li>1. Adopt a national approach to <b>newborn screening</b></li> <li>2. Implement <b>early detection and preventive services</b> across Canada</li> </ol>
<p><b>Goal #2: Providing timely, equitable and evidence-informed care</b></p> <ol style="list-style-type: none"> <li>3. Improve education and capacity of <b>healthcare providers</b> related to rare diseases, including genetic counsellors</li> <li>4. Address <b>gaps in social care programs</b> for people with rare disorders</li> <li>5. Develop provincial guidelines to ensure <b>appropriate accommodation</b> for people with rare diseases in the <b>workplace</b></li> <li>6. Provide people with rare diseases the same <b>coverage for healthcare services</b> (e.g., physiotherapy) as people with more common diseases</li> <li>7. Establish <b>Centres of Excellence on rare diseases</b> to generate and support research and patient care, develop and implement clinical practice guidelines, develop and provide professional and patient education to general healthcare practitioners and the public, and develop and support extended diagnostic, clinical and educational services, for example, through telemedicine or satellite specialized clinics</li> <li>8. Explore the creation of a <b>national registry for all rare diseases</b>, and support new and existing <b>disease-specific registries</b></li> <li>9. For diseases where specialized clinics and virtual clinical networks may not be feasible, ensure better integration of care for patients with rare diseases into existing <b>Complex Care Clinics or medical homes</b></li> <li>10. Adopt measures to facilitate <b>linkages between healthcare administrative databases</b> across the country to support health service delivery to patients with rare diseases</li> </ol>
<p><b>Goal #3: Enhancing community support</b></p> <ol style="list-style-type: none"> <li>11. <b>Rare disease-specific patient organizations</b>, as well as <b>CORD and the RQMO</b>, should be <b>adequately funded</b> to achieve their missions, which include involvement in research initiatives, knowledge translation, policy development, education, engagement and support initiatives for patients</li> <li>12. Increase resources to optimize the utility of <b>Orphanet for all stakeholders</b></li> </ol>
<p><b>Goal #4: Providing sustainable access to promising therapies</b></p> <ol style="list-style-type: none"> <li>13. Implement a <b>regulatory framework</b> for orphan drugs</li> <li>14. Explore <b>adaptive clinical trial designs</b> for market authorization and post-market phases of therapies</li> <li>15. Enhance and formalize the <b>role of patients in the market authorization process</b> and post-market evidence-generation and provide resources to support the participation of rare disease patient groups in this process</li> <li>16. Establish a <b>separate, more flexible health technology assessment process</b> tailored to the specific attributes of orphan drugs</li> <li>17. Provide increased <b>support to assist rare disease patient groups in engaging in health technology assessment reviews</b>, including in preparing patient input submissions</li> <li>18. Develop a consistent <b>funding approach</b> to ensure timely and equitable patient access to orphan drugs</li> </ol>
<p><b>Goal #5: Promoting innovative research</b></p> <ol style="list-style-type: none"> <li>19. Provide <b>dedicated and increased funding for rare disease research</b> and the Centres of Excellence on rare diseases</li> <li>20. Establish a new <b>Canadian Partnership for Rare Diseases</b> to help coordinate a national rare disease research agenda and Centres of Excellence on rare diseases, among other actions recommended throughout this strategy</li> </ol>

*“At 33, I finally got a diagnosis, but not soon enough to spare my 2-year-old daughter who was diagnosed with the same genetic condition. But we started her on therapy right away so hopefully she’ll never suffer the way I did.”*

Ian, 34-year-old man with Muckle-Wells

## Strategy for Improving the Lives of Canadians with Rare Diseases

### Goal #1: Improving early detection and prevention

#### Context

Although 80% of rare diseases are genetic and can now be accurately identified, this reality is far from the possibility. **According to CORD's survey,<sup>3</sup> approximately two out of five respondents said that their rare condition was genetic,<sup>4</sup> but almost none of those respondents said that they had received any pre-natal counselling or screening.** In addition, respondents experienced considerable delay and difficulty in obtaining a correct diagnosis, receiving, on average, **two to three “wrong” diagnoses.** While one-fourth got their diagnosis in less than three months, **one-third struggled for more than three years, and it took more than six years to obtain a correct diagnosis for one-fifth of respondents.**

A number of tools and tests are available to help identify, detect and sometimes prevent rare diseases with a genetic cause:

- ***Newborn screening:*** Since screening for phenylketonuria (PKU) using a heel-prick dried blood spot sample taken in the first few days after birth was introduced in the mid-1960s, the development and implementation of similar screening tests have saved thousands of lives in Canada. Newborn screening is currently available in most provinces; however, standards and criteria vary across the country. In September 2014, provincial and territorial health ministers recognized newborn screening as a critical tool to improve health outcomes for children by identifying disorders before the onset of symptoms. The health ministers recommended that provincial and territorial officials “continue to develop an evidence-based list of recommended primary newborn conditions for pan-Canadian use.”<sup>5</sup> Subsequently, the Canadian Agency for Drugs and Technologies in Health (CADTH) was awarded a grant to convene a task force to study and recommend a national approach to newborn screening.
- ***Next-generation diagnostic testing:*** Next-generation sequencing is emerging as a comprehensive and efficient approach to the identification of genetic contributions to rare diseases but is not yet readily available in most Canadian jurisdictions.
  - ***Diagnosis:*** International studies have now demonstrated that approximately 30% of previously undiagnosed rare genetic diseases can be diagnosed using this approach and the Canadian College of Medical Geneticists has issued a position statement on this approach.<sup>6</sup> An early molecular diagnosis informs patient management and facilitates screening of at-risk family members for the presence of the same rare disease.
  - ***Carrier screening:*** Although carrier screening for certain rare diseases (e.g., hemoglobinopathies) is standard practice for high-risk populations in Canada, next-generation sequencing approaches will facilitate a more broad risk

<sup>3</sup> CORD Patient Survey conducted January – March 2015; n = 491 English / 61 French.

<sup>4</sup> One fourth of respondents did not know whether their condition was genetic.

<sup>5</sup> <http://www.scics.gc.ca/english/conferences.asp?a=viewdocument&id=2217>

<sup>6</sup> <http://www.ncbi.nlm.nih.gov/pubmed/25951830>

assessment for the general population, thereby enabling reproductive options for carrier couples.

## Gaps

- Awareness among parents of the potential value of pre-conception screening is low. Genetic screening and counselling for family members prior to conception is essential to ensure parents are able to make well-informed decisions.
- Consistent and comprehensive guidelines for healthcare professionals regarding available and recommended genetic testing would help improve screening, early detection, and prevention.
- The causes and natural progression of many rare diseases are not yet understood. Expanded initiatives directed towards understanding the cause and natural progression of many rare diseases are needed in order to inform the development of strategies for screening, early detection and possible prevention.

## Actions

- 1. Provincial and territorial governments must work together to adopt a national approach to newborn screening.** This approach should include:
  - a. A coordinated genomics approach that includes new analytical methodologies and technologies for screening, such as next generation DNA sequencing and new mass spectrometric methods
  - b. New sample types, such as dried saliva and fetal DNA in maternal blood
  - c. New informatics systems to integrate genomic and metabolomics results
  - d. Optimal number of test sites guided by efficiency and sufficiency of number of tests interpreted to ensure expertise
  - e. Frameworks to ensure that newborn screening programs comply with ethical and legal standards, including privacy standards
  - f. Health information systems to ensure timely access for healthcare providers who must implement therapies to respond to screening information generated at different time points (e.g., prenatally, early infancy, or in late childhood)
  - g. An evaluative framework to assess the benefits, harms and costs of the implementation of new screening modalities and strategies
  - h. Guidelines for using and sharing results from newborn screening that protects the rights and wishes of families while serving the public good
  - i. Appropriate training for healthcare providers to optimize use of newborn screening
- 2. Provincial and territorial governments should collaborate to implement appropriate early detection and preventive services across the country that include comprehensive next-generation screening and appropriate approaches to diagnose rare diseases with no genetic link.** Examples of how this could be implemented include:
  - a. ***Implementation of next-generation sequencing technologies into the diagnostic care algorithm for patients with suspected rare genetic diseases.*** To be most effective, this approach should include linkages to national infrastructure for coded data sharing, such as PhenomeCentral,<sup>7</sup> an international

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<sup>7</sup> See <https://phenomecentral.org>

repository for secure data sharing among clinicians and scientists working on identifying the cause of rare genetic diseases.

- b. ***Timely and appropriate access to screening, testing and counselling*** and ***education and support materials*** for patients and family members (especially those with known family histories of genetic disorders) to guide patient decision-making.

*“Surgery and radiation did not successfully remove the tumour causing my rare disorder. Treating the tumour resulted in other rare conditions for which medications are generally not covered. After a long battle, coverage was obtained for one medication, but a new drug that could treat the tumour is not yet available in Canada. So the fight by our patient community continues.”*

Tracy, 44-year-old mom with Cushing’s Disease

## Goal #2: Providing timely, equitable and evidence-informed care

### Context

Patients with rare diseases struggle to obtain timely and quality clinical and social care. More specifically, they experience difficulties in obtaining adequate and useful information about their condition. Based on CORD's Survey, **the information and support patients received at the time of diagnosis and afterwards are woefully inadequate.** Two out of five respondents did not get the right amount of information and only three in five respondents felt they understood the information provided by the doctor. Most lacking were follow-up education and support, with **two-thirds reporting they were given no person or contact number for additional information, and the same proportion reporting that they were not referred to a patient organization.** Given all of these challenges, it is not surprising that a significant majority of survey participants said that family doctors were not informed about rare diseases. More problematic was the overwhelming perception among survey respondents that neither paediatricians nor specialists were well informed about rare diseases.

Outlined below are areas or initiatives that should be leveraged to help improve the care provided to people living with rare disorders.

### *Training healthcare professionals*

Education of health professionals in Canada has historically been siloed; however, the rise of inter-professional education in recent years has shown promise for improving the integration and coordination of care. The University of Manitoba, for example, uses inter-professional models<sup>8</sup> of teaching to integrate multiple health disciplines, health research and integrated service delivery models.

### *Clinical practice guidelines*

A key part of informing and educating healthcare professionals is developing and implementing clinical practice guidelines (CPGs) to guide the treatment of rare diseases. CPGs comprise recommendations on the care of patients with specific conditions, based on the best available research, evidence, and practice/experience. While methods to develop CPGs exist, their development is resource-intensive so there is a tendency to focus on common diseases. In Canada, there has been little development of CPGs for rare diseases. The development of CPGs for rare diseases is hindered by limited knowledge of the natural progression of most rare diseases, heterogeneity across patients with the same disease, limited specialist expertise, and the lack of good evidence on treatment effects. In the Canadian context, there are treatment guidelines for certain rare diseases, including hemophilia<sup>9</sup> and Von Willebrand disease for patients seen within the haemophilia comprehensive care centres,<sup>10</sup> PKU,<sup>11</sup> and Prader-Willi Syndrome.<sup>12</sup> However, as of today, most treatment guidelines focus on:

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<sup>8</sup> [http://umanitoba.ca/faculties/health\\_sciences/medicine/6755.html](http://umanitoba.ca/faculties/health_sciences/medicine/6755.html)

<sup>9</sup> <http://www.hemophilia.ca/files/ComprehensiveCareStandards-EN.pdf>

<sup>10</sup> <http://ahcdc.ca/index.php/membership/practice-guidelines/86-hemophilia-and-vwd-clinical-practice-guidelines-management>

- Specific types of cancer (e.g., myelodysplastic syndrome<sup>13</sup>)
- Specific procedures (e.g., genetic testing of inherited cardiac arrhythmias associated with Sudden Cardiac Death<sup>14</sup>)
- Drugs for specific cancer sub-populations (e.g., Bortezomib in multiple myeloma and lymphoma<sup>15</sup>)
- Specific procedures or activities (e.g., physical activity for children with juvenile idiopathic arthritis, hemophilia, asthma and cystic fibrosis<sup>16</sup>)

Internationally, there have been several initiatives to develop CPGs that Canadian healthcare providers and policy-makers may engage with or adapt to the Canadian context. The European Union conducted a four-year study (RARE-Best practices)<sup>17</sup> and launched a related project in 2014 to catalyze the development of CPGs for rare diseases. Within Europe, France has defined a method to develop guidelines for rare diseases. Orphanet has also developed guidelines for the emergency treatment of rare diseases.<sup>18</sup>

### ***Disease registries***

Clinicians can improve their knowledge of rare disease patterns and care of patients with rare diseases through rare disease registries. A rare disease registry contains information on patients who have been diagnosed with a specific rare disease. These registries can be used by clinicians and researchers to better understand patient populations, respond to emerging healthcare issues, assess variability in care and treatment choices across provinces, develop quality improvement initiatives, and track clinical outcomes over time. These efforts will ultimately translate into better health outcomes for patients with rare diseases. Some disease-specific registries have been established in Canada by patient groups (e.g., the Cystic Fibrosis Patient Registry<sup>19</sup>), industry (e.g., the Genzyme Rare Disease Registry,<sup>20</sup> which encompasses Pompé, Gaucher, MPS1 and Fabry) and researchers (e.g., the Canadian Fabry Disease Initiative<sup>21</sup>). Several are linked internationally, increasing their potential value, such as the Canadian Neuromuscular Disease Registry,<sup>22</sup> a Canada-wide registry of individuals diagnosed with a neuromuscular disease, which participates in the international Translational Research in

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[https://www.acmg.net/docs/Phenylalanine\\_Hydrosylase\\_Deficiency\\_Practice\\_Guideline\\_AOP\\_Jan\\_2013.pdf](https://www.acmg.net/docs/Phenylalanine_Hydrosylase_Deficiency_Practice_Guideline_AOP_Jan_2013.pdf)

<sup>12</sup> <http://www.fpwr.org/wp-content/uploads/2014/02/2008clinicalGuide.pdf>

<sup>13</sup> <http://www.saskcancer.ca/MDS>

<sup>14</sup> <http://www.ncbi.nlm.nih.gov/pubmed/21459272>

<sup>15</sup> <https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34323>

<sup>16</sup> CPS Position Statement: Physical activity recommendations for children with specific chronic health conditions: Juvenile idiopathic arthritis, hemophilia, asthma and cystic fibrosis

<sup>17</sup> [http://www.rarebestpractices.eu/documenti/newsletter/newsletter\\_1.pdf](http://www.rarebestpractices.eu/documenti/newsletter/newsletter_1.pdf)

<sup>18</sup> These emergency guidelines include a short description of the disease, recommendations for immediate care, transport and orientation before getting to the emergency ward (identifying potential complications, diagnostic and therapeutic particularities, drug interactions and anaesthesia issues), recommendations for the patient's and family's comfort, and a 24-hour list of contacts. [http://www.orpha.net/consor/cgi-bin/Disease\\_Emergency.php?lng=EN](http://www.orpha.net/consor/cgi-bin/Disease_Emergency.php?lng=EN)

<sup>19</sup> <http://www.cysticfibrosis.ca/cf-care/cf-registry/>

<sup>20</sup> <http://www.genzyme.com/Products/Resources-for-Health-Care-Professionals.aspx>

<sup>21</sup> <http://www.the-cfdi.ca>

<sup>22</sup> <http://www.cndr.org/>

Europe – Assessment & Treatment of Neuromuscular Diseases Neuromuscular Network (TREAT-NMD)<sup>23</sup> and contains data on over 2,400 Canadian adults and children affected by over 40 different rare diseases.

Disease registries are widely regarded by patients as useful tools in improving care and treatments and improving access to research opportunities. Joint principles to guide the development of rare disease registries have been agreed upon by CORD, the American National Organisation for Rare Disorders (NORD), and the European Organisation for Rare Diseases (EURORDIS),<sup>24</sup> which includes interoperability and harmonization between individual registries, a minimum set of Common Data Elements, and inclusion of data reported by patients and by health professionals.<sup>25</sup>

In Canada, as elsewhere, challenges exist as to the ownership of patient registries, their sustainability, and potential conflicts of interest in terms of sponsorship. While these issues are far from resolved, all stakeholders increasingly agree that multiple proprietary registries are counterproductive and are moving toward collaborative solutions that include all.

Robust disease registries also catalyze research into safe and effective therapies for rare diseases, provide tools for regulators and payers (e.g., provincial governments and insurance companies) to track real-world outcomes of therapies for rare diseases, and support the development of comprehensive care services for patients with rare diseases. Further registries provide an obvious choice for long-term post-marketing surveillance of rare disease therapies and technologies.

### ***Comprehensive care services***

There are few rare disease clinics in Canada and even fewer with comprehensive care services. It is not surprising that **over half of the CORD Survey respondents feel they do not get access to specialists or clinics and there is little coordination of care.**

Canada does have some successful models of integrated and coordinated care, such as paediatric metabolic centres. Of the 17 academic paediatric centres across Canada, 13<sup>26</sup> have on-site multidisciplinary metabolic teams for the diagnosis and treatment for children and/or adults with rare and ultra-rare inborn errors of metabolism (i.e., complex inherited metabolic disorders). These metabolic teams vary in size and composition and include physicians, genetic counsellors, dietitians, pharmacists, social workers, psychologists, nurses and administrative staff. The metabolic teams are all strongly aligned with laboratory scientists who direct the metabolic and molecular laboratories that provide direct support to the clinical metabolic services. Other successful examples

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<sup>23</sup> [http://cordis.europa.eu/project/rcn/84926\\_en.html](http://cordis.europa.eu/project/rcn/84926_en.html)

<sup>24</sup> <http://www.eurordis.org/content/eurordis-nord-cord-release-joint-declaration-10-key-principles-rare-disease-patient-registries>

<sup>25</sup> In another European initiative, the European Platform for Rare Disease Registries (EPIRARE), a three-year European Commission program, produced guidelines for data sources and quality for registries for rare diseases. See <http://www.epirare.eu>

<sup>26</sup> These 13 centres include all centres except the Northern Ontario School of Medicine, Nunavut, NWT and Yukon. The care of children and families with metabolic genetic disorders in centres without metabolic teams generally falls under the jurisdiction of one of the existing teams in closest geographic proximity.

of coordinated care for rare diseases include hemophilia comprehensive care centres<sup>27</sup> and cystic fibrosis (CF) clinics.<sup>28</sup> Across Canada, there are 25 hemophilia comprehensive care clinics, each staffed by a hematologist, nurse coordinator, physiotherapist, psychologist or social worker, a data manager and other specialists as needed. Patients go to the hemophilia clinic in person only once or twice a year for routine assessments, but stay in regular contact by telephone, email, electronic infusion reporting systems and other telehealth tools. Following the creation of these clinics, musculoskeletal health and quality of life have improved dramatically and emergency room visits have become a rarity. CF clinics, present in most major cities, provide specialized multidisciplinary care for individuals with CF within a hospital setting. Various healthcare professionals see CF patients at each clinic visit and during hospitalization. Individuals attend clinic visits three to four times annually to consult with clinic team members, including physicians, nurses, dietitians, physiotherapists, social workers, pharmacists, and others.

### ***Centres of excellence and virtual clinical networks***

Given that rare diseases affect small numbers of patients and are often heterogeneous, severe and poorly understood, collaboration and coordination of expertise is essential for their efficient diagnosis and management. Centres of excellence and virtual clinical networks have been successfully implemented in Europe to provide all patients with a particular rare disease the same quality of care, regardless of where they reside. Europe has diverse models: some centres and networks are specific to one disease while others span all rare diseases; some focus on delivering health services only while others also undertake research. Many have achieved sustainable funding, with at least part of the funding provided by European Union member states. The European Union has developed criteria for centres of excellence.<sup>29</sup>

The wide geographical dispersion of both patients with rare diseases and clinical experts in Canada has motivated the increasing recognition of centres of excellence and virtual clinical networks as necessary components of high quality care. The House of Commons Standing Committee on Health recognized the importance of such models in the context of rare diseases in its June 2013 report,<sup>30</sup> *Technological Innovation in Health Care*:<sup>31</sup>

*Canadian Institutes of Health Research and the Public Health Agency of Canada, in collaboration with the Networks of Centres of Excellence, [should] consider identifying clusters of rare disease in Canada, and consider formalizing some of them as Centres of Excellence within the Network.*

Currently, there are few such centres and networks in Canada. The Maternal Infant Child & Youth Research Network,<sup>32</sup> which has rare diseases as part of its program, provides one example. Centres of excellence can serve as the cornerstone of health service delivery for patients with rare diseases by coordinating patient registries, developing

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<sup>27</sup> <http://www.hemophilia.ca/en/treatment-centres/>

<sup>28</sup> <http://www.cysticfibrosis.ca/cf-care/how-cf-care-is-delivered-in-canada/cf-clinics-in-canada/>

<sup>29</sup> <http://www.raredisease.org.uk/documents/Website Documents /centres-of-excellence-10-a4.pdf>

<sup>30</sup> <http://www.parl.gc.ca/HousePublications/Publication.aspx?DocId=6221741&Language=E&File=9>

<sup>31</sup> *Technological Innovation in Health Care*, Report of the Standing Committee on Health, June 2013:

<http://www.parl.gc.ca/content/hoc/Committee/411/HESA/Reports/RP6221741/hesarp14/hesarp14-e.pdf>

<sup>32</sup> <http://www.micyrn.ca>

and implementing standards of care and treatment guidelines, providing quality clinical care, and enhancing information for professionals and patients.

### ***Social care***

The needs of many patients with rare diseases extend beyond healthcare support and access to treatments. Psychosocial services, recreational and physical therapy, counselling, respite care and special education are often required. In general, these services have not been included as benefits recognized as essential to the management of rare diseases across Canada. The exception may be rare cancers: most provinces have dedicated resources and programs for all cancer patients, rare and common, which span many of these services. For nearly all other rare diseases, since many of the services are non-medical or fall outside of the *Canada Health Act*, there is no legislation that obliges governments to offer them, unless they become political priorities.

Rare diseases often place a profound burden on individuals and families and, with few exceptions, there is a lack of specialized and/or accessible social services, such as therapeutic recreation programs and respite care. This stems, in part, from a lack of awareness among providers of social services. Many rare diseases have limited medical interventions (of 7,000 known rare diseases, fewer than 5% have effective therapeutic interventions)<sup>33</sup> and many require on-going care. As noted in the CORD survey, most community-based services (such as education, disability and employment) are perceived as having little awareness or knowledge about rare diseases, making access to services limited. Worse, when patients and families apply, there are challenges to recognizing their needs because the disease may not be identified as one eligible for assistance or other benefits.

People with rare diseases often qualify for the federal Disability Tax Credit and thus receive some financial assistance. However, the success of these applications depends as well on the knowledge base of the healthcare provider and his or her willingness to support such an application.

Outreach to the education system has been a key activity for many rare disease groups, often stimulated by parents who want to be assured that the teachers and schools were aware of and supportive of their children's special needs. The education and intervention may take many forms, including providing children with the resources to explain their condition, arranging for special assistance as needed, and ensuring medical precautions and emergency procedures are in place. Recently, one Canadian mother of a child with Prader-Willi Syndrome who is also a special education resource teacher, launched a new initiative to help parents engage schools as advocates and become "champions" for the development of individualized education plans for their children.

Thanks to better knowledge and healthcare, many children with rare diseases who would have died prior to adulthood are now surviving, such as those with Duchenne muscular dystrophy or CF. These individuals require ongoing special assistance, which, for the most part, does not exist in the Canadian healthcare and social services systems. One enterprising mother has worked with the charity Partners for Planning<sup>34</sup> to create a

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<sup>33</sup> [http://www.phrma.org/sites/default/files/pdf/Rare\\_Diseases\\_2013.pdf](http://www.phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf)

<sup>34</sup> <http://hub.partnersforplanning.ca>

guide and identify resources for parents of adult children that will enable them to plan for their child's future and create a "lifetime personal network of safety, security and love."

## Gaps

- Healthcare providers do not have adequate information about the treatment and management of rare diseases.
- Providers of social care, education services, disability services, and employers often do not understand the impacts of living with a rare disease and programs are not available to rare disease patients.
- While it may not be feasible to create a Canadian database for each disease, a national registry for all rare diseases should be established and the number of rare disease-specific registries should be increased. In all cases, efforts should be made to link Canadian patients to the international community in order to facilitate the creation of a global database.
- The development and maintenance of patient registries are inadequately coordinated and supported in Canada.
- Canada has not yet established criteria for centres of excellence in rare diseases, and the European Union criteria are not applicable in the Canadian context.
- There is a lack of specialized clinics to provide appropriate care to patients with rare diseases.
- Measures to facilitate links between healthcare administrative databases across the country to support health service delivery to patients with rare diseases are needed.

## Actions

- 3. Provincial and territorial governments should collaborate with health professional regulatory colleges and associations, universities and colleges, and academic hospitals to improve education and capacity of healthcare providers related to rare diseases, including:**
  - a. An inter-professional model of health professional education with a specific component on rare diseases to improve awareness and enhance integrated care of patients and families.
  - b. Enhanced capacity, recruitment and training of healthcare professionals and professionals in related disciplines, such as genetic counselling, research, laboratory medicine and social work, working with rare diseases.
  - c. Taking advantage of curriculum renewal to integrate training on rare diseases.
  - d. Involving individuals, families and patient organizations in the development of new teaching approaches.
- 4. Provincial and territorial governments should review criteria for social care programs (including education and disability services) and make appropriate changes where necessary to ensure equitable access to services for people with rare disorders.**
- 5. Provincial and territorial governments should develop guidelines for employers in providing appropriate accommodation for people with rare diseases in the workplace.**

6. Private insurance companies and provincial and territorial governments should, where coverage exists for specific services for patients with common diseases (e.g., physiotherapy for a mobility limitation), extend that same coverage to patients with rare diseases.
7. Centres of Excellence on rare diseases should be established to generate and support research and patient care, develop and implement clinical practice guidelines, develop and provide professional and patient education to general healthcare practitioners and the public and develop and support extended diagnostic, clinical and educational services, for example, through telemedicine or satellite specialized clinics. These Centres would be supported by federal agencies, including CIHR and the Public Health Agency of Canada as well as provincial and territorial governments.
8. Centres of Excellence on rare diseases in partnership with governments, industry, patient organizations and other health system leaders should explore the creation of a national registry for all rare diseases and support new and existing disease-specific registries with harmonized datasets to facilitate data sharing and collaboration. These registries should adopt the following principles and best practices:
  - a. The principles set out in the joint declaration of principles signed by CORD, NORD, and EURORDIS
  - b. Where applicable, adhere to the Canadian Neurological Registry Best Practice Guidelines<sup>35</sup>
  - c. A minimum set of Common Data Elements necessary for meaningful collaboration and sharing of data, which focus on the disease rather than an intervention
  - d. A process to integrate with existing electronic medical records that are available in paediatric hospitals and all specialty clinics, to link to relevant biobanks, and capture data from patients and families, as well as healthcare providers
  - e. Clearly-defined rules regarding governance, ownership, sponsorship, and access to information
  - f. Shared infrastructure to harmonize data and minimize costs
  - g. International links with applicable registries and databases
9. For conditions where specialized clinics and virtual clinical networks are not feasible, provincial and territorial governments should ensure better integration of care for patients with rare diseases into existing Complex Care Clinics or medical homes as they can provide important support for patients with rare diseases.
10. Provincial and territorial governments should adopt measures to facilitate linkages between healthcare administrative databases across the country to support health service delivery to patients with rare diseases.

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<sup>35</sup> <http://canadianregistrynetwork.org>

*“When you grow up thinking monthly blood transfusions and nightly 10-hour drug infusions are ‘normal,’ almost anything else is possible. A rare disease isn’t limiting if you have treatment, but most importantly the support of family and friends.”*

Cassandra, 16-year-old girl with Thalassemia Major

## Goal #3: Enhancing community support

### Context

The rare disease community is instrumental in providing support, connecting patients to resources and one another, communicating information about rare diseases to policy and decision-makers, the media and the public, and ensuring that patient voices are heard. This diverse community is made up of many stakeholders, including patients, patient organizations, health and social care service providers and researchers.

In particular, Canada has many rare disease-specific patient organizations. They provide opportunities for patients to connect with other patients who share similar experiences and are, in some cases, the only source of relevant and useful information on disease management and care. Most rare disease patient organizations are founded by a patient or family member and are volunteer-based. In addition to supporting rare disease patients and their families, these groups also carry out advocacy, awareness and fundraising activities. While patient charities and non-profit groups are willing to carry out these activities, they require linkages into existing public programs and on-going support in order to be available and effective. In many cases, the key challenge for these initiatives is their success, often publicized through social media, so that the demand far outstrips the capacity of volunteer-based groups to sustain and expand to meet growing needs.

The scope of the activities, infrastructure and available support for rare disease patient organizations varies. As a result, CORD,<sup>36</sup> a national umbrella organization for over 100 rare disease patient organizations, individual patients and other stakeholders, and the RQMO,<sup>37</sup> at the provincial level, function as coordinating bodies for communicating information about rare diseases and ensuring that patient perspectives are heard.

Over the past decade, CORD has taken the lead in promoting policies, programs and services that serve the rare disease patient community, often bringing together stakeholders, initiating policy discussions, hosting consultations and developing briefs, providing training and skills-development to patients and patient groups and raising awareness among policy makers, providers and the public to stimulate change and reform. The RQMO has served similar functions in Quebec. Both CORD and RQMO engage regularly with EURORDIS.<sup>38</sup> CORD is recognized as a leading patient alliance at the international level and has taken on the role of bringing Canadian and international stakeholders and initiatives together on a periodic basis to share, learn from one another and to create even more synergy.

The main challenge for most rare disease patient organizations, CORD and RQMO is access to sustainable funding. Few patient organizations receive financial support from public or private granting sources. While large patient organizations focusing on common diseases have the resources and capacity to pursue private funds, those focused on rare diseases often do not.

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<sup>36</sup> <http://www.raredisorders.ca>

<sup>37</sup> <http://rqmo.org/wp/>

<sup>38</sup> <http://www.eurordis.org>

Finally, while there has been an initial compilation of a list of Canadian patient organizations and other rare diseases resources on the Orphanet portal, the information is still being compiled. Orphanet is a potentially useful source of information for patients and families living with a rare disease and can serve as an information portal for knowledge exchange, collaboration, and support between both small and umbrella organizations. However, additional support is required to increase awareness of the Canadian portal on the Orphanet website among patient organizations and other potential users.

## Gaps

- There is inadequate funding for small rare disease patient groups. Many of these organizations have limited resources to support patients while also carrying other tasks, such as networking with relevant Canadian and international patient organizations, sponsoring and/or administering disease registries, identifying high-quality research and well-trained and interested researchers and raising awareness about related rare diseases.
- Collaboration, coordination and development of patient groups through CORD and RQMO are very effective but hampered by the lack of dedicated and sustainable resources to these umbrella organizations.
- The Canadian Orphanet database is still incomplete and its sustainability is uncertain as a result of the absence of dedicated funding.

## Actions

- 11. Rare disease-specific patient organizations, as well as CORD and RQMO, should be adequately funded to achieve their missions, which include involvement in research initiatives, knowledge translation, policy development, education, engagement and support initiatives for patients.**
- 12. Orphanet should be adequately resourced to serve as the portal and resource network serving all stakeholders in the rare disease community.**



*“I have an ultra-rare blood disease that leads to kidney failure. The only effective therapy is a drug approved by Health Canada but denied by the provincial public drug plans because of its high cost. This disease destroyed my own kidneys as well a transplanted kidney donated by my wife. The doctors won’t allow another transplant unless I’m on this drug. What’s really frustrating is that my province refuses to approve this drug for transplants. So I must remain on dialysis.”*

Michael, 50-year-old with aHUS

## Goal #4: Providing sustainable access to promising therapies

### Context

Over the past 30 years, research and development related to rare diseases has led to the development of many promising therapies. Much of this research was supported internationally by orphan drug policies and legislation that encouraged investment in the research and development of treatments for rare diseases and their reimbursement.

In Canada, however, patients with rare diseases often experience difficulties and delays in accessing treatments. CORD's survey shows that **one in three respondents could not access appropriate drug treatments**. As more fully explained in this section, there are a number of reasons why there are challenges in accessing treatments in this country, including:

- Lack of a regulatory framework to encourage the development and timely approval of orphan drugs in Canada
- The national health technology assessment process used by public drug plans to decide whether to fund treatments does not take into account the specific attributes of orphan drugs
- There is no consistent funding approach for orphan drugs to ensure that patients across the country have access to the treatments that they need
- Decision-making on reimbursement is protracted and delayed, often with access criteria that are much more restrictive than the labeled indications.

#### *(i) Regulatory framework*

In Canada, drug authorization is regulated under the federal *Food and Drugs Act*, which does not, at the present time, include any definition or specific process for treatments for rare diseases. This means that the regulatory requirements, including evidence requirements, for these treatments are the same as those for common diseases. At the international level, many jurisdictions, such as the European Union,<sup>39</sup> the United States,<sup>40</sup> Japan,<sup>41</sup> Australia<sup>42</sup> and Taiwan<sup>43</sup> have implemented regulatory frameworks for orphan drugs. These frameworks help encourage research and development of orphan drugs, which can be very challenging due to:

- Small, dispersed patient populations
- The profound diversity of rare disease pathology (most is still unknown)
- Significant clinical heterogeneity even within a single rare disease making it difficult to stratify by stage and severity

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<sup>39</sup> *Regulation EC No. 141/2000*: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

<sup>40</sup> *Orphan Drug Act*:

<http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdca/significantamendments-to-the-fdca/orphan-drug-act/default.htm>

<sup>41</sup> *Pharmaceutical Affairs Law*: [http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan\\_drug.html](http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html)

<sup>42</sup> *Therapeutic Goods Regulations*: [http://www5.austlii.edu.au/au/legis/cth/consol\\_reg/tgr1990300/](http://www5.austlii.edu.au/au/legis/cth/consol_reg/tgr1990300/)

<sup>43</sup> *Rare Disease Control and Orphan Drug Act*:

[http://www.tfrd.org.tw/english/laws/cont.php?kind\\_id=25&top1=What%20we%20do&top2=Public%20Policy%20Issues&top3=Rare%20Disease%20and%20Orphan%20Drug%20Act](http://www.tfrd.org.tw/english/laws/cont.php?kind_id=25&top1=What%20we%20do&top2=Public%20Policy%20Issues&top3=Rare%20Disease%20and%20Orphan%20Drug%20Act)

- The lack of validated biomarkers and surrogate endpoints
- A lack of predictive and validated pre-clinical in vitro and animal models
- The scarcity of clinical experts and reference centres
- Inadequate regulatory procedures neither adapted to the evolution of science nor shared at an international level
- Methodological bottlenecks and difficulty in designing studies that are both clinically valid and aligned with regulatory requirements

In the fall of 2012, the federal minister of health announced plans<sup>44</sup> for developing an orphan drug framework for Canada. The minister stated that the government “*will introduce a new approach that will better support the development and authorization of drugs for rare diseases...*”. This framework is expected to address the designation, authorization and monitoring of orphan drugs using a life-cycle approach, and focusing on international information-sharing and collaboration. It will also involve greater patient engagement in regulatory activities related to orphan drugs.

The federal orphan drug regulatory framework drafted by Health Canada<sup>45</sup> proposes the first official definition of “rare disease” in Canada, which is crucial to aligning various policies throughout the country on a common understanding. This definition is similar to the one adopted by the European Union (5 in 10,000 individuals) in an effort to harmonize regulatory approval processes internationally.

In 2014, regional multi-stakeholder fora were held across the country to gather initial feedback on the elements of the proposed framework and Health Canada piloted a process to invite patient submissions on two rare disease drugs as part of the regulatory review, with the goal of making this a standard option under the new orphan drug regulatory framework. However, timelines for implementing the orphan drug regulatory framework remain unclear.

With regard to clinical trials more specifically, CORD believes that trials for rare diseases should be conducted with high methodological standards, including a strong – though unconventional – statistical rationale. There may be a need, however, to reconsider the guidance and standards concerning trials for rare disease therapies. In recent years, many have recognized that the guidance and standards used for drugs for more common diseases may not be appropriate for rare diseases and have begun to examine alternative requirements for drugs targeting small populations. More specifically, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada are all considering the use of “adaptive trial designs,” which are methods of designing a clinical trial where different elements of the trial, such as sample size, the number of treatment arms, or the rate at which participants are randomized, may be modified while generating statistically sound data. Although the exploration of adaptive clinical trials is not limited to drugs for rare diseases, such trial designs accommodate many of the unique challenges of generating evidence on the efficacy of these drugs. This approach suggests that a regulatory decision may not be a one-time event, but

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<sup>44</sup> [http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/\\_2012/2012-147-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2012/2012-147-eng.php)

<sup>45</sup> Health Canada, Office of Legislative and Regulatory Modernization, *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework*, December 13, 2012: <http://www.raredisorders.ca/documents/RegulatoryFrameworkDraft.Dec2012copy.pdf>

could evolve as interim analyses are done, additional evidence generated and designs modified.

In terms of patient involvement, the EMA and its counterpart regulatory bodies in Australia, New Zealand, Canada and the United States accept patient-reported outcomes (PROs) for clinical trials of all drugs, and include patients in discussions around them. The EMA provides patients groups with resources and funding for participation in its committees and activities.

Patient involvement in PROs is also occurring outside of the regulatory environment. An example is the development of a clinical outcome measure for Batten disease. This measure was subsequently incorporated into clinical trial protocols by regulatory agencies. The US Patient-Centered Outcomes Research Institute (PCORI),<sup>46</sup> established in 2010, aims to ensure that its work “is inclusive of an individual’s preferences, autonomy, and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life”.<sup>47</sup> In Canada, the CIHR issued a Strategy for Patient-Oriented Research (SPOR)<sup>48</sup> in the fall of 2011. The importance of patient involvement in developing relevant outcome measures is emphasized in this Strategy:<sup>49</sup>

*There is also emerging interest in patient reported outcomes, in addition to clinically reported outcomes. This is a huge emerging area of study in the United States and Europe. The concern is that clinical trials focused on particular medical endpoints and not on the patient experience with drugs and devices might result in an efficacious drug being designed that brings with it a quality of life or personal cost too great to warrant the use of the drug. An example is provided by people with AIDS, first in the United States and then in the United Kingdom, who challenged researchers’ approaches to conducting trials which had overlooked patients’ preferred outcomes.*

Although neither PCORI’s nor CIHR’s initiatives are intended for rare diseases specifically, it is expected that they will be part of the agenda for action.

Patient groups have had a less formal and accepted role in the generation of evidence in the post-market, real-world stage. Nevertheless, they are intimately involved in generating evidence as part of the treatment protocols for most rare disease drugs, which require patients to participate in regular post-market monitoring, including blood and other tests, reporting of symptoms and adverse events, tracking outcomes through diaries or other tools and completing surveys measuring, for example, impact and quality of life indicators. Patient groups – particularly rare disease patient groups – are poorly resourced to collect and analyze evidence, as most are small, volunteer-based, and poorly funded. At the international level, for instance, the European Union funds EUPATI (European Patients Academy in Therapeutic Innovation),<sup>50</sup> a training program managed by a patient-led consortium to prepare individuals and groups to be effective advocates

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<sup>46</sup> <http://www.pcori.org>

<sup>47</sup> <http://www.pcori.org/research-results/patient-centered-outcomes-research>

<sup>48</sup> <http://www.cihr-irsc.gc.ca/e/47473.html>

<sup>49</sup> [http://www.cihr-irsc.gc.ca/e/documents/P-O\\_Research\\_Strategy-eng.pdf](http://www.cihr-irsc.gc.ca/e/documents/P-O_Research_Strategy-eng.pdf)

<sup>50</sup> <http://www.patientsacademy.eu/index.php/en/>

and advisors in medicines research (e.g., in clinical trials, with regulatory authorities and on ethics committees).

## Gaps

- There is no official definition of “rare disease” to act as a starting point for discussions and alignment of policies across the country.
- Health Canada’s draft orphan drug regulatory framework has not yet been implemented. This framework is needed to encourage the development and authorization of orphan drugs in Canada.
- Rare disease patient groups are poorly resourced to collect and analyze evidence to provide their input as part of the regulatory process, as most are small, volunteer-based and poorly funded.

## Actions

**13. Health Canada should immediately implement the regulatory framework for orphan drugs.**

**14. Health Canada, in collaboration with researchers, health technology assessment (HTA) bodies, public and private payers, patients, healthcare professionals and industry, should further explore adaptive clinical trial designs for market authorization and post-market phases of therapy, building upon initiatives taking place in Europe with the EMA, EUnetHTA (serving the European HTA Network), industry and patient organizations, and in the United States through the FDA’s initiatives for Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review.**

**15. Health Canada should enhance and formalize the role of patients in the market authorization process and post-market evidence-generation and provide resources - including training, support, and financial assistance - for rare disease patient groups to collect, analyze and synthesize evidence and to participate in the regulatory process.**

## *(ii) Health technology assessment*

### Context

Uncertainty in clinical effectiveness tends to be higher for therapies for rare diseases as supporting evidence is usually generated through smaller clinical studies. The cost per patient of these therapies is also often higher given the small patient population and the fact that the majority of these therapies are lifetime therapies. As a result, these therapies frequently receive negative recommendations from advisory committees of the CADTH-based Common Drug Review (CDR) and pan-Canadian Oncology Drug Review (pCODR). Provincial governments and hospitals also have their own HTA bodies to provide guidance on their reimbursement decisions (e.g., the Ontario Committee to Evaluate Drugs). For patients, a negative review can be devastating, as many of them rely on public drug plans to obtain these therapies, which are often their only option for improving their health outcomes.

Since its inception, HTA has relied on principles and methods to guide drug evaluations. These principles and methods, however, assume access to large patient populations and an in-depth understanding of the clinical epidemiology of a condition. This presents a significant challenge for treatments that target rare diseases.

While CADTH considered whether to establish a separate HTA process tailored to therapies for rare diseases, it decided in 2014 that these therapies would essentially be evaluated pursuant to the same principles and methods as drugs for common diseases.<sup>51</sup> Only small process changes were made to accommodate orphan drugs, such as the possibility for increased involvement of outside experts. As well, the Institut national d'excellence en santé et en services sociaux (INESSS), Quebec's HTA agency, has not yet adopted a specific evaluation process for orphan drugs.

Internationally, many countries are increasingly recognizing the limitations of applying standard HTA processes and principles to orphan drugs and are opting to modify their approaches. In the United Kingdom, a separate pathway for “highly specialized technologies” has been created.<sup>52</sup> Many ultra-orphan drugs would meet the criteria established for eligibility through this pathway. Some jurisdictions have adopted flexible approaches by accepting, for instance, more uncertainty in the economic appraisal of orphan drugs and a higher than usual cost per quality-adjusted life year in certain cases.<sup>53</sup> Others have developed safety net programs through which orphan drugs may be reviewed.<sup>54</sup>

With regard to patient involvement in drug assessments, CADTH opened a pathway in 2009 for patient submissions to the CDR, as did the Ontario Committee to Evaluate Drugs. Patient groups are asked to collect evidence from their members about their opinions on current therapies, unmet needs and the new therapy under review.

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<sup>51</sup> CDR Update Issue 103, May 2014: <https://www.cadth.ca/cdr-update-issue-103>

<sup>52</sup> <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance>

<sup>53</sup> For example, the Scottish Medicines Consortium. See <http://rarejournal.org/rarejournal/article/view/60>

<sup>54</sup> For example, Australia's Pharmaceutical Benefits Advisory Committee. See [https://www.cadth.ca/media/pdf/ES0281\\_RareDiseaseDrugs\\_es\\_e.pdf](https://www.cadth.ca/media/pdf/ES0281_RareDiseaseDrugs_es_e.pdf)

Subsequently, pCODR as well as other provinces (British Columbia and Quebec) introduced options for patient input. CADTH also recently launched a pilot process to enable individual patients and caregivers to provide input where there is no related patient group (e.g., in the case of small disease population). Many of these HTA bodies have put together guides and templates to help patient groups develop their submissions. However, patient groups, especially those dedicated to rare diseases, require more guidance, funding and training to optimize their submissions. Internationally, for instance, the United Kingdom's HTA agency, the National Institute for Health and Care Excellence (NICE)<sup>55</sup> as well as the Scottish Medicines Consortium<sup>56</sup> provide support to facilitate patients' involvement.

## Gaps

- HTA processes in Canada do not adequately recognize the limitations of evidence that can be generated for orphan drugs. More flexible methodological approaches are needed to assess therapies for rare diseases in Canada.
- Patient groups – particularly rare disease patient groups – are poorly resourced to collect and analyze evidence for the purposes of drug evaluations, as most are small, volunteer-based and poorly funded.

## Actions

16. CADTH and INESSS should establish separate, more flexible evaluation processes that are tailored to the specific attributes of orphan drugs.
17. CADTH and INESSS should provide dedicated staff (e.g., patient navigators), training, and funding to assist patient groups to better engage in the HTA processes, including support in preparing patient input submissions.

### *(iii) Funding*

#### Context

Often, patient access to treatments is limited by inadequate or unavailable funding. **The CORD survey shows that two in five respondents do not have private drug plans and that those with private drug plans are not fully covered. Nearly a third said their prescription drugs were not covered by their drug plan and the same proportion responded that the costs and/or the co-pays made the drugs inaccessible to them.**

Despite the lack of burden of illness studies for rare diseases in Canada, specific studies in other countries have indicated that costs may be 7 to 16 times higher for a rare disease as compared to more common ones, with correspondingly higher impact on families. The CORD Survey also confirmed that **nearly three in four patients and**

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<sup>55</sup> <http://www.nice.org.uk/media/default/About/NICE-Communities/Public-involvement/PIN/NICE-PIN-memorandum-of-understanding-November-2013.pdf>

<sup>56</sup> <http://www.gov.scot/Publications/2014/07/4751/5>

**families incur significant personal costs** in dealing with their rare disease. **Families spend, on average, more than \$10,000 on disease-related costs that are not covered by the public or private health plans.**

### *Private health insurance plans*

The Canadian Life and Health Insurance Association (CLHIA) has tried to ensure that the specific and diverse needs of patients and families living with rare diseases are accommodated in benefit plans that cover appropriate treatments and supports. Since the cost of some of these treatments can be high and may be unsustainable for some plans, CHLIA has introduced risk-pooling across insurance companies to help mitigate the impact of drug costs.<sup>57</sup>

### *Public health insurance plans*

Currently, provinces such as Alberta,<sup>58</sup> British Columbia,<sup>59</sup> Ontario<sup>60</sup> and New Brunswick<sup>61</sup> have implemented specific policies and programs that provide access to certain orphan drugs for eligible patients. In addition, once CADTH issues a reimbursement recommendation, provincial governments frequently rely on agreements negotiated with manufacturers under the pan-Canadian Pharmaceutical Alliance (pCPA) for those therapies.<sup>62</sup> Cost savings have been reported as a result of pCPA negotiations. Although there are different perspectives on the pCPA and its process, this approach may help improve the availability of orphan drugs in Canadian provinces.<sup>63</sup>

While these initiatives have helped facilitate reimbursement of certain orphan drugs, there is currently no consistent funding approach to ensure that patients across Canada can access new promising therapies. Although risk-pooling has been discussed collectively by the public payers in Canada, currently there are no plans to implement such an approach. In 2014, provincial and territorial ministers created a working group led by Alberta, British Columbia and Ontario that will explore ways to manage the cost of rare disease drug therapies using evidence-based approaches.<sup>64</sup> However, progress made to date on this work as well as timelines for next steps, including the potential adoption of an approach to funding orphan drugs, remain unclear.

### *Managed access programs*

Managed access programs (MAPs) could help facilitate patient access to orphan drugs. Specifically, MAPs enable the introduction or use of promising technologies that, due to a variety of reasons, are deemed to have an inadequate evidence base for widespread

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<sup>57</sup> Canadian Drug Insurance Pooling Corporation:  
[http://www.clhia.ca/domino/html/clhia/CLHIA\\_LP4W\\_LND\\_Webstation.nsf/page/1E92C4ED60A4002F852579CA00678818!OpenDocument](http://www.clhia.ca/domino/html/clhia/CLHIA_LP4W_LND_Webstation.nsf/page/1E92C4ED60A4002F852579CA00678818!OpenDocument)

<sup>58</sup> <http://www.health.alberta.ca/documents/Pharma-Strategy-2008-rare-disease.pdf>

<sup>59</sup> BC Ministry of Health Expensive Drugs for Rare Diseases Advisory Committee

<sup>60</sup> [http://www.health.gov.on.ca/en/pro/programs/drugs/eap\\_mn.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/eap_mn.aspx)

<sup>61</sup> [http://www2.gnb.ca/content/gnb/en/services/services\\_renderer.201352.New\\_Brunswick\\_Drugs\\_for\\_Rare\\_Diseases\\_Plan.html](http://www2.gnb.ca/content/gnb/en/services/services_renderer.201352.New_Brunswick_Drugs_for_Rare_Diseases_Plan.html)

<sup>62</sup> <http://www.pmprovincesterritoires.ca/en/initiatives/358-pan-canadian-pricing-alliance>

<sup>63</sup> <http://healthydebate.ca/2014/10/topic/cost-of-care/pan-canadian-pharmaceutical-alliance>

<sup>64</sup> <http://www.scics.gc.ca/english/conferences.asp?a=viewdocument&id=2217>

use. These programs, which are negotiated between manufacturers and payers, provide access to a therapy with a requirement for additional specific data to be collected to fill an evidence gap. In a Summit on Access to Drugs for Rare Disease in Canada organized by CORD in July 2014, participants from different stakeholder communities agreed that managed access might be a viable approach to some, though not all, orphan drugs.

However, there is little publicly available information on the outcomes of any MAPs that have been implemented in Canada because they are usually based on confidential agreements between manufacturers and payers. On the international scene, a study published in 2013 concluded that such programs have been used in seven European countries to manage the uncertainty associated with orphan drugs.<sup>65</sup>

Data collection as part of MAPs is often done through patient registries and allows for subsequent review and determination of the appropriate patient population for the treatment. Patient registries for such a purpose can be either established to chart the natural history of the rare disease or created specifically for an individual drug or drugs for a particular disease. While many registries are established with funding from manufacturers, some rare disease organizations have also, as previously mentioned in this document, created their own registries. There are numerous design and operational challenges involved with the creation of registries, and multiple stakeholder perspectives need to be taken into account. Considerable work has been undertaken internationally to address some of these challenges, specifically in the rare disease area, and could be used to build approaches for Canada.

## Gaps

- There is no consistent funding approach to ensure that patients with rare diseases across the country can access the therapies that they need in a timely fashion. While the provinces have established a working group to explore funding approaches for orphan drugs, the status of this work and timelines for implementing a potential approach remain unclear.
- While MAPs could offer a viable option to address economic or clinical uncertainty relating to orphan drugs, there is limited data on their use and outcomes in Canada.

## Actions

**18. The provinces, territories and the federal government should collaborate to develop, in consultation with stakeholders, a consistent funding approach that ensures timely and equitable patient access to orphan drugs.**

- a. As part of this work, governments could explore the use of MAPs as a way to facilitate patient access while addressing uncertainties. Specifically, a study may be commissioned to examine the use and outcomes of MAPs in Canada.

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<sup>65</sup> Morel et al., “Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries”, Orphanet Journal of Rare Diseases, 8:198, 2013: <http://www.ojrd.com/content/8/1/198>



*If you think finding the gene for a previously undiagnosed rare disease is exciting, imagine unlocking the genetic codes for 146 rare diseases! This unprecedented success was achieved in just two years by Dr. Kym Boycott and her co-investigators through an innovative study, Finding of Rare Disease Genes (FORGE), funded by Genome Canada and CIHR. And now they're looking for treatments based on those discoveries.*

Durhane Wong-Rieger, CORD President and CEO

## Goal #5: Promoting innovative research

### Context

The research-based identification and understanding of rare diseases and development of diagnostic and therapeutic options will significantly reduce global public health costs and the burden of disease while improving the quality of life for those suffering from a rare disease. Rare disease research not only increases our understanding of other rare diseases, given their shared challenges, but can also contribute to the understanding of more common diseases leading to therapeutic options for these conditions. One example of the broader impact of rare disease research is the introduction of Infliximab with an initial indication for an orphan disease, Crohn's disease, and the subsequent approval of this therapy for common diseases (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis and plaque psoriasis). As we move forward in the era of personalized medicine, experience and knowledge gained through rare disease research will benefit more common diseases.

While Canada's rare disease research community is rich, with the exception of a number of large-scale multi-center projects, it is fragmented and limited in terms of pan-Canadian coordination. Often, important results generated through rare disease research do not make it to clinical application. There is also a gap in the knowledge exchange between academic and industry research, ultimately failing in the translation of research discoveries and effective progress towards therapeutic solutions.

In Canada, there currently exist enormous pre-clinical rare disease research strengths both in terms of molecular diagnostics and the pathogenic elucidation that follows rare disease gene identification. Canada benefits from open and inclusive research, strong international collaborations and a research capacity that spans the research continuum, including basic biomedical research, clinical research and health services and policy research. These strengths should be leveraged in the field of rare disease research. There are shining examples of national networks and international leadership in rare disease research, including collaborative research community, cutting edge "omics" platforms, model systems, high calibre researchers and their networks.

### Gaps

- There is a strong need to foster collaborative programs in all fields of rare disease research, from fundamental, basic research to clinical and social research, engaging all stakeholders.
- A lack of effective therapies to treat an increasing numbers of patients diagnosed with rare disorders.
- Lack of patient involvement in developing outcome measures relevant to their specific rare diseases and the acceptable benefit-harm trade-offs, especially in the post-market phase of evidence-generation.
- Lack of studies on disease etiology and natural history or progression of most rare diseases that account for their heterogeneity.
- Lack of research into best methods for conducting clinical trials as well as health systems and quality of life is critical for improving the lot of the Canadian rare disease community.

- There are few high-quality studies on the burden of illness of rare diseases in Canada. Burden of illness studies are essential to understanding the impact of the management of rare diseases on patients, families, and the broader community.

## Actions

**19. The federal and provincial and territorial government should collaborate with the private sector to provide dedicated and increased funding for rare disease research and the Centres of Excellence on rare diseases.**

**20. A new Canadian Partnership for Rare Diseases – funded by federal, provincial and territorial governments – should be established to help coordinate a national rare disease research agenda, among other actions recommended throughout this strategy.**

a. **Priorities of the research agenda** could include:

- i. Establishing the rare disease etiology (usually genetic) on as many rare diseases as possible
- ii. Developing improved screening and diagnostic techniques, including clinical whole exome/genome sequencing
- iii. Determining the rare disease incidence, prevalence, clinical nosology and natural history
- iv. Enhancing basic research for increased pathogenic insight
- v. Developing and evaluating new standards of care, medical devices, and effective therapeutics
- vi. Enhancing clinical research to trial novel interventions, and their most efficacious applications
- vii. Stimulating social and human research related to the needs of rare disease patients studying the burden of illness of rare diseases on the Canadian society

b. **Activities of the Partnership** could include:

- i. Coordination of the activities and sharing of best practices among the Centres of Excellence on rare diseases
- ii. Establishment of specific research platforms and infrastructure, including generalized therapeutic approaches
- iii. Management of access to data and biological samples for regional, national and international collaborations
- iv. Aid for the development of clinical trial expertise and infrastructure, including methodological approaches for rare disease therapies
- v. Establishment of national and international networks facilitating clinical trials of the appropriate design and size
- vi. Stimulation of research on new or existing orphan drugs
- vii. Help promoting collaboration among clinicians, geneticists, epidemiologists, and patients to improve knowledge on different aspects of rare diseases and ensure research translation
- viii. Establishment of better linkages of research and industry efforts in the area of rare diseases
- ix. Creation of recruitment and training programs to attract talent in rare disease research and provide additional incentives for young scientists as well as rare disease training for researchers at all stages of their careers

- x. Coordination with national and provincial funding agencies fellowship programs directed to graduate students, PhD, post-doctoral researchers and group leaders in the rare disease field
- xi. Development of public outreach involving scientific and medical awareness and communication activities, such as courses and workshops, conferences, practical courses, symposia and lectures, as well as other types of training media (e.g., e-learning)
- xii. Ensuring that patients are active partners in rare disease research, as they hold much of the information, can help organize campaigns for the donation of biological samples and disseminate research results to the community.



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