FINDING THE MISSING PIECE

A VISION FOR RARE DISEASE CARE IN CANADA

RARE i
THE CANADIAN FORUM FOR RARE DISEASE INNOVATORS

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EXECUTIVE SUMMARY

Rare diseases affect more than three million Canadians. They take a tremendous toll on families, health systems, and society. And yet, Canada is well behind many other countries when it comes to caring for people with rare diseases.

However, with growing awareness of these challenges and a $1.5 billion funding commitment from the federal government, Canada now has a unique opportunity to create one of the best health systems in the world to test for, diagnose and treat rare diseases.

At this point, there is one crucial piece missing. What is needed now, more than ever, is political will from federal, provincial, and territorial government leaders to move forward on rare disease strategies and funding.

Canadians also need to be ambitious when it comes to designing a system that delivers the best results for patients.

What might that look like? Here is RAREi's three-point vision:

1. **Better access to therapies:** Patients need better and faster access to medicines that can save or improve their lives. For this, a special system needs to be designed for reviewing rare disease medicines, taking into account the unique characteristics of these treatments. Patients should be able to benefit from safe and effective treatments immediately following Health Canada approval, without making them wait for additional value assessments and price negotiations.
2. **Improved care pathways:** Current rare disease care pathways are difficult to understand and navigate, for patients and care providers alike. The system can be made much faster and easier to access by creating rare disease centres across Canada (similar to current cancer centres), to provide specialized care and treatment.
3. **Focused on results for patients:** All too often, health care systems prioritize bureaucracy and administrative processes over the well-being of patients. Canada needs to embrace value-based health care, which rewards quality (improved results for patients) rather than quantity (volume of services delivered).

This vision paper reviews the current state of rare disease care in Canada and uses key learnings and successes from other countries to provide some important lessons for Canada as it builds its own much-needed enhanced services for Canadians with rare diseases.

STATEMENT FROM THE CHAIR OF RAREi

RAREi is a network of 18 Canadian biopharmaceutical companies committed to improving the lives of Canadians with rare diseases by researching, developing and commercializing rare disease treatments.

Our companies share a commitment to Canadians with rare diseases – to develop and bring to them the best available treatments for their conditions and to continue to work to discover and develop new treatments where none existed before.

We can't do that alone. We need – Canadian patients need – a complete environment that acknowledges the special requirements of rare diseases and their treatment that is part of but different in important ways from that created for managing the common health challenges Canadian face.

In this paper RAREi outlines its three-point vision for achieving that new environment for the better care of Canadians with rare diseases. Patients and their families need better access to therapies, improved care pathways and a system focused on delivering results for patients.

The good news is we believe these three points are all readily achievable because we have all the foundational pieces in place. What we need is political will to make it happen.

This paper shows how we can do just that to make life better for the three million Canadians with a rare disease and their loved ones.

Bob McLay
Chair, RAREi
Vice-President, General Manager Canada, Sobi Canada

The member companies of RAREi are:

- Alexion Canada
- Amicus Therapeutics
- Argenx Canada
- Astellas Canada
- Biogen Canada
- Biomarin Pharmaceutical
- Boehringer Ingelheim Canada
- GlaxoSmithKline Canada
- Horizon Therapeutics
- Ipsen Canada
- Janssen Canada
- Mitsubishi Tanabe Pharma Canada
- Recordati Rare Diseases
- Sanofi Canada
- Sobi Canada
- Takeda Canada
- Ultragenyx Pharmaceutical Canada
- Vertex Canada

INTRODUCTION

Rare diseases are a relatively common problem, affecting millions of Canadians directly or indirectly and having a large effect on Canada's health systems.

Different countries and groups define rare diseases in different ways, using different numbers. But whatever the numbers used, all definitions of rare diseases mean they are illnesses that affect relatively few people compared to those that are clearly widespread, such as heart disease, cancer, lung disease, diabetes, and arthritis.

Some conditions that affect very few people are called ultra-rare diseases, some of which are known to affect even fewer than 10 Canadians. For example, the genetic neurodegenerative disorder spastic paraplegia 50 (SPG50) has only one known patient in Canada.[1]

The Canadian Organization for Rare Disorders (CORD) defines a rare disease as a condition affecting fewer than one person in 2,000 in their lifetime. There are more than 7,000 known rare diseases and dozens more being discovered each year. In total, CORD estimates one out of every 12 Canadians will be affected by a rare disease. However, about two-thirds of these are children, so their condition has a huge impact on parents and extended families, meaning millions of additional Canadians are affected by rare diseases less directly.[2]

Because each rare disease affects only a small number of individuals, understanding and expertise for a given rare disorder may be limited and fragmented across the country. Individual physicians may go their whole career without seeing a single case of many of these conditions.

About 80% of rare diseases are caused by genetic changes, which explains why such a large percentage of people with rare diseases are children. Unfortunately, despite recent medical and treatment advances, according to CORD, one in every four children with a rare disease will not live to see their 10th birthday.[3]

Right now, CORD data show that only 60% of treatments for rare disorders are made available in Canada and most get approved up to six years later than in the United States and Europe.[4] As a result, many people with rare disorders in Canada are missing out on treatments that could save or significantly improve their lives. The proposals in this paper aim to change this situation.

Of the approximately 7,000 rare diseases, there are effective treatments for fewer than 10% of these conditions.[5] Even with the incentives offered by the U.S. Orphan Drug Act, fewer than 15 new treatments for rare diseases are approved in that country per year (see more about the Orphan Drug Act in Section VI). It has been determined that on average it takes nearly four years longer to develop a rare disease treatment compared with medicines to treat more common conditions and another study found that just 6% of such medications in development get approved, half the 12% rate for new products overall.[6]

Fewer of those new treatments are approved in Canada. And even when an effective treatment has been developed and approved, patients must still endure lengthy waits and great uncertainty as to whether they will be able to access these treatments in this country.

Many of these conditions are severely debilitating or life-threatening and the affected patients and families face many challenges living with these conditions. RAREi believes that a compassionate health care system should be organized in such a way as to ensure timely and reasonable access to needed therapies.

CURRENT CHALLENGES TO TIMELY DIAGNOSIS AND TREATMENT IN CANADA

This section looks at the state of rare diseases in Canada and outlines some of the key challenges affecting timely diagnosis and treatment.

A) Health system challenges

Results from a survey of more than 500 Canadians with rare diseases and their caregivers by Ipsos and published by CORD in February 2023 provide useful insights into the current state of rare disease diagnosis and treatment in Canada and the impact of the challenges in the current system on Canadians managing rare diseases.

Patient and caregiver respondents clearly felt that their health care professionals lacked knowledge of rare diseases, which delayed diagnosis and specialist care. Four out of five (80%) said they do not think family physicians are aware and informed about rare diseases and 62% say the same about pediatricians.

Almost half (47%) do not believe specialists have up-to-date knowledge about rare diseases.[7]

The process of getting an accurate diagnosis is long and difficult, the survey showed, with respondents saying they waited an average of 3.7 years to get an accurate diagnosis and, in the process, saw an average of 5.9 different health care professionals and received an average of 3.2 wrong diagnoses.

Rare diseases also place a large burden on families and other caregivers. According to a national survey conducted by CORD in 2019, two-thirds of Canadians caring for someone with a rare disease feel unsupported by Canada's health care system.[8] As well, the vast majority (87%) have had their family finances negatively affected as a result of their responsibilities, three out of four are socially isolated and almost 80% suffer from mental health issues as a result of their caregiving responsibilities.

B) Lack of a distinct regulatory framework for rare diseases

Contrary to most other developed countries, Canada does not have a distinct regulatory framework for rare disease treatments. Consequently, many of these treatments come to Canada later or do not come to Canada at all. Specifically, according to one study, submissions to Health Canada for 84% of rare disease treatments approved between 2002 and 2016 were filed after these submissions were filed with American and European regulators.[9]

The reason behind this is that there are currently very few incentives for launching treatments in Canada. Most developed countries have established distinct regulatory frameworks to help incentivize the development and commercialization of rare disease therapies. These frameworks typically include a definition of rare disease, an orphan product designation process, strengthened intellectual property or additional data protection, and other financial incentives such as research promotion funds, tax incentives and regulatory submission fee reductions.

Unfortunately, Canada does not have any of these special incentives. To clarify, RAREi is not supportive of any reforms that would compromise Health Canada's current high review standards, rather it is seeking modifications that would support and incentivize the development and introduction of effective rare disease treatments in Canada.

C) Issues with Canada's Special Access Programme

Canada's Special Access Program (SAP) for medicines is crucial for patients because it allows expedited access to potentially life-saving or critical medications that are not yet approved for general use. At present, patients seeking access to treatments that are not approved by Health Canada must rely on their clinicians to help them navigate the SAP. Although initially designed as an exceptional mechanism, the SAP has become the de facto treatment access pathway for many rare disease patients due to the fact that the treatments they need are not available commercially through the standard access pathway.

Of the almost 500 medicines approved by the SAP in 2016, 29% were for treatments classified as orphan medications in the jurisdictions where they were already approved. In addition, 50% of the SAP medications were first approved by the programme 10 years previously.[10]

The SAP is not an ideal mechanism for facilitating access to rare disease treatments. It is a time-consuming process that requires patients to rely on their clinician to seek customized approval from Health Canada by providing scientific literature demonstrating that a given treatment that is available elsewhere in the world is the right solution to meet that patient's particular needs. Even when this process is followed successfully, often the initial authorization expires within six months (or less) and patients must work with their clinicians to undergo the process all over again. Worse still, Health Canada's

approval does not come with reimbursement, leaving patients to figure out how to pay for their treatment.

Due to limitations in the Canadian pharmaceutical review and approval process, some manufacturers may rely on the SAP to facilitate access while circumventing the need to pursue a formal Health Canada submission. RAREi does not believe that the SAP should not be used by manufacturers seeking to achieve Canadian market authorization through a reduced regulatory standard. This scenario could put potential competitive products, which are introduced via the formal process, at a disadvantage. So, while it is important to ensure that rare disease patients are not cut-off from accessing products on the SAP when there are no other therapeutic options and little chance that a given manufacturer will submit to Health Canada, it is important for the system to ensure manufacturers are not discouraged from seeking formal market authorization through the standard process.

D) Challenges related to clinical trials for rare diseases

Clinical trials are essential for patients as they provide access to cutting-edge innovations that may not yet be available through standard care. There is no disputing that randomized clinical trials (RCTs) are the gold standard for evaluating the efficacy and safety of medications. However, a key issue related to clinical trials for rare disease treatmnets is that in most cases they are not feasible because the number of available patients is so low or they are unethical because treatment for a potentially life-threatening condition cannot be denied simply to generate trial data.

Another challenge to conducting traditional clinical studies is that few clinicians are familiar with rare diseases. This, of course, impacts patient care but it also makes it challenging to recruit knowledgeable physicians to administer clinical trials.

A further potential issue is the limited understanding of many rare diseases and their natural course without treatment, compounding challenges to be able to effectively evaluate the impact of any given treatment.

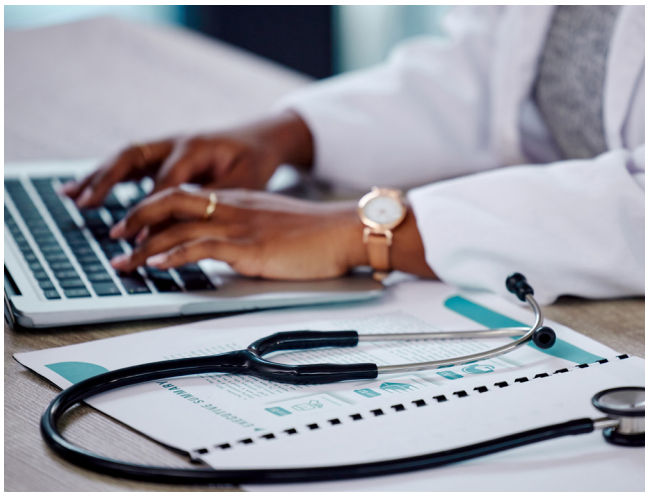
Alternative clinical trial design methodologies that enable the study of rare disease treatments create greater uncertainty for regulators, health technology assessment (HTA) evaluators and those involved in the reimbursement process. While regulators have made great strides in understanding this type of data, innovators routinely face challenges when presenting study results in the context of HTAs due to the rigid evaluation framework.

In response, regulators have worked with researchers and innovators to evolve trial designs that are specifically suited to rare diseases and innovative therapies. These ne approaches ensure that reviewers are able to rigorously evaluate the evidence available and recommend continued data collection, often in real-world use, to extend the findings. The challenge then becomes one of ensuring appropriate monitoring and collection and analysis of real-world data.

E) Health technology assessment of rare disease treatments

Following Health Canada's regulatory review and approval, new treatments are subject to HTA by the publicly funded Canadian Agency for Drugs and Technologies in Health (CADTH) for all jurisdictions except Quebec, which has its own body, the Institut national d'excellence en santé et services sociaux (INESSS). These evaluations consider the appropriate use of the therapies in real-world settings as well as the socioeconomic impact of the new treatment relative to the added benefit compared with existing therapies and the submitted price to make recommendations which then guide the subsequent pricing and reimbursement negotiations with public drug plans.

However, despite recent indications of a willingness by HTA reviewers to make efforts to consider rare disease treatments more expansively, the current HTA review process fails to account for the unique characteristics of rare disease treatments, including the small size of clinical trials and the fact that RCTs are often not possible for life-threatening conditions. In addition, CADTH reviews are not flexible enough to accommodate informed therapeutic and/or current patient management knowledge in a specific therapeutic area or for a given condition.



Further, many experts have recognized the limitations of current cost-effectiveness methods when evaluating rare disease treatments.[11] These methods were designed to be used in broad population-based assessments and they do not work well when considering treatments developed to meet the needs of small populations and that have higher per-patient price. Also, these methods are intended to compare the value of a new medicine with the value of an older medicine, which is often impossible to do with rare disease breakthrough treatments, as many do not have appropriate comparators.

Since the traditional HTA methods were never designed for rare disease treatments, these medicines often fail to meet the required cost-effectiveness thresholds which leads to HTA recommendations for these treatments that often include the suggestion that substantial price reductions (up to 97%) are required to meet the cost-effectiveness thresholds.[12] Despite therapeutic value being recognized by the assessment, the associated recommendations make it very hard for rare disease treatments to be successfully negotiated and reimbursed by public drug plans, which means patients are deprived of timely access to these treatments.

F) Reimbursement agreement delays

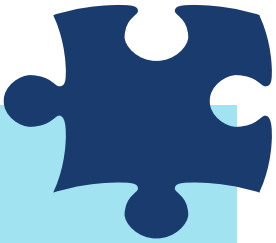
Following HTA evaluation, the next step in the public reimbursement process is negotiations between the manufacturer and the pan-Canadian Pharmaceutical Alliance (pCPA), which represents the federal and provincial/territorial public drug plans. Before a medicine can be reimbursed by public drug plans, the reimbursement terms of a new medicine have to be negotiated through the pCPA process.

There are many challenges with this process that negatively affect patient access to all new medicines, not just those for rare diseases. The process can take anywhere

between a few months to several years (the average timeline in 2017-18 was approximately a year following the finalization of a CADTH recommendation). [13] Further, even once an agreement has been reached with the pCPA, there is no guarantee that public plans will add the medicine to their formularies or that they will do so in timely manner. This is because there is no requirement for public plans to reimburse the medicine and no set timeline for reimbursement following the successful conclusion of a pCPA agreement.

As a result, Canada ranks 15th out of 20 developed countries when it comes to wait times between regulatory approval of a medicine and its reimbursement by public plans.[14] As well, there is a significant difference in reimbursement timelines between public and private drug plans in Canada. According to one study, private plans take on average 142 days to cover new medicines following Health Canada's approval compared with 449 days for public drug plans.[15]

These challenges relating to public reimbursement are even more complex when it comes to medicines for rare diseases, given the lack of appropriate HTA assessment methods for these treatments. This means that vulnerable patients, such as those with a rare condition, may not be able to access the treatments they need or may have to wait much longer to access life-saving treatments.



CASE STUDY
A CANADIAN TREATMENT UNAVAILABLE TO CANADIANS

Fibrodysplasia ossilicans progressiva, or FOP, is a very rare genetic condition where, starting at birth and progressing with age, muscles and tendons are transformed into bone, starting with the neck and shoulders then into the limbs. Movement is painful and ultimately impossible, and over time patients can be trapped inside a "second skeleton," often resulting in early death. It's a form of stiff person syndrome, the illness which Céline Dion recently announced she contracted.

A new therapy for FOP was discovered and researched by a small Montreal biotech company, Clementia Pharmaceuticals. The medicine, Sohonos, was acquired by the France-based Ipsen Pharma, a global biopharmaceutical company with the resources to develop it and support its use by patients beyond clinical trials. Sohonos was submitted to Health Canada, where it received priority review on April 15, 2021, and was approved nine months later, on Jan. 21, 2022 — the first country to approve Sohonos for treatment of FOP.

But more than a year after approval, not a single Canadian patient had been granted access to it. All applications to the public drug plans had been denied.

STEPS TOWARD A RARE DISEASE STRATEGY FOR CANADA

The issues related to the treatment of rare diseases in Canada are well known. In recent years, several concrete steps have been taken towards a better rare disease strategy for Canada.

CORD Rare Disease Strategy 2015

CORD developed and announced its proposed rare disease strategy in 2015 and has been working diligently since then to have it adopted. [16] It has continued to discuss and revise its ideas as a result of developments during the ensuing years, but the core elements and objectives remain the same:

- Improve early detection and preventing the disease or preventing progression
- Get the right care to patients as early as possible
- Enhance community support, providing sustainable access to promising therapies and promoting innovative research

The strategy also calls for centres of excellence and a new Canadian partnership for rare diseases, with the former modeled on other centres of excellence that have been established in other sectors to promote change and progress.

Federal 2019 budget commitment and public consultation

A major result of the activities of CORD and other stakeholders to improve the state of rare disease treatment in Canada was the announcement by the federal government in its 2019 budget that it would commit new spending of $500 million per year for at least two years starting in 2022-23 towards the cost of providing Canadians with treatments for rare diseases.

2023 federal funding announcement

In March 2023, the federal government announced a three-year, $1.5 billion investment aimed at boosting access to and

affordability of rare disease medicines.[17] The strategy committed $1.4 billion for provincial and territorial governments through bilateral agreements to improve access to new and emerging products; $33 million to the Indigenous Services Canada's Non-Insured Health Benefits (NIHB); and $68 million to improve data collection, enhance research and clinical trials, and support national governance structures (including the creation of a stakeholder implementation advisory group to support the implementation of the strategy).

Of note, the announcement did not include a definition of a "rare disease." Health Canada officials indicated that this will be considered in discussions with provinces in the context of developing criteria to determine a "small set of new and emerging drugs" to cover. Officials also specified they would look at definitions in other jurisdictions (such as Europe) to guide this work.

Importantly, there has been limited progress on finalizing bilateral agreements between the federal government and the provinces and territories, which is needed to start the rollout of the funding for new and emerging treatments.

Provincial developments

- The **Quebec** government launched its provincial rare disease policy in June 2022.[18] The policy outlines a framework for optimizing the accessibility of quality health care and services that are safe, fair, inclusive and adapted to the specific needs of an estimated 700,000 rare disease patients in the province and their families. It includes a definition of rare diseases as one affecting fewer than one in 2,000 people and a vision to "Optimize access to quality health care for rare disease patients." Its three themes are 1) awareness building and training, 2) ensuring equitable access to diagnosis and care and 3) promoting research, innovation and data collection. Under the policy, an action plan with a funding commitment as well as an evaluation plan to track commitments will be developed and an advisory committee was set up to prepare the action plan.
- In **Ontario**, the previous Liberal provincial government established a rare disease implementation plan steering committee in December 2017 to implement certain recommendations from a rare disease working group that had issued its report in March 2017.[19] With the change in Ontario government in June 2018 and then the COVID-19 pandemic, there has been no further formal government progress related to rare diseases. However, Life Sciences Ontario (LSO) has been advocating strenuously for a rare diseases strategy for Ontario, including through the release of a 2021 vision paper outlining five actions "to create a provincial rare disease strategy to save lives and boost Ontario's economy."[20] Furthermore, in June 2023, three New Democratic Party members of provincial parliament introduced a private

members' bill calling on the government to "as soon as is practicable, implement the recommendations set out in the rare diseases working group report, dated March 10, 2017."

- In **British Columbia**, while the province says the BC PharmaCare Program "may provide exceptional funding, on a case-by-case basis, for 'expensive drugs for rare diseases,'" the process is very challenging, requiring that it "be carefully reviewed to ensure that the medication is effective for each person being treated." And even before that, the treatment must undergo the same review as for other PharmaCare products but with an additional patient review process. In the end, the province says, "The Ministry decides which eligible drugs and indications are to be considered for case-by-case funding." With this process, it adds, it "ensures that the PharmaCare program remains fair, effective and sustainable." [21]

- The **Alberta** government pays relatively little attention to rare disease treatments in its public drug programs, with its notice from 2008 saying only that, "Selected drug products used in the treatment of rare diseases may be considered for coverage for individuals covered under Alberta government-sponsored drug programs." The program launched in April 2009 and covered treatments for just five rare diseases.[22] There have been some additions since, such as in December 2021 when it was announced that a second gene therapy used to treat spinal muscular atrophy would also become available in Alberta through the rare diseases drug coverage program after a pricing agreement was reached through the pCPA in October 2021.[23]

- In June 2023 at the BIO International convention in the U.S., **Manitoba** launched what it called a "visionary new life sciences strategy."[24] One of the provisions of the new strategy is its noting that biotech companies face several issues, including market access. As a result, the strategy says that, "To improve access and collaboration, the Manitoba government will establish dedicated resources within Manitoba Health to support innovative industry partnerships that improve the health care of all Manitobans."[25] No specifics are given.

- While not created for rare disease treatments, in **New Brunswick** one of the province's two health authorities, the Horizon Health Network, announced at the BIO meeting in June 2023 that it would offer cancer patients early access to selected new Health Canada-approved treatments as part of an agreement with Amgen Canada.[26] This agreement marks the first time in several years that one of the pCPA participating jurisdictions has agreed to reimburse products before they have been through all the steps of the Canadian medication review and approval process . It is a potential indicator of the type of faster access process that could be provided in Canada for new rare disease treatments. What could work for one company's cancer treatments in one province could potentially work for all treatments for rare diseases across Canada.

HOW OTHER COUNTRIES MANAGE RARE DISEASE DIAGNOSIS AND TREATMENT

Other countries have unique approaches to rare diseases, and it is useful to consider whether and how such initiatives could be adopted or adjusted for use in Canada.

One of the key things to bear in mind is that Canada remains a serious laggard with few programs in place to meet the needs of Canadian with rare diseases.

AUSTRALIA

Australia has implemented various initiatives to support rare disease management, including creating the Australian Genomics Health Alliance, a collaborative network of researchers, clinicians and patients aiming to improve diagnosis and treatment for rare diseases through genomic research. It supports government-funded genomic research projects, distils research outcomes to inform policy and practice, and progresses national standards for genomic data management. [27]

Additionally, the Australian Therapeutic Goods Administration, the Australian government authority responsible for evaluating, assessing and monitoring medicines, medical devices and biologicals, has a specific pathway called the Special Access Scheme (SAS) that allows patients with life-threatening conditions, including rare diseases, to access unapproved therapies. The SAS provides a mechanism for early access to treatments before they receive full regulatory approval.[28]

BELGIUM

Belgium has been a leader in developing and maintaining a comprehensive Central Registry of Rare Diseases, a database containing basic data of all Belgian patients with a rare disease. At present, data is collected only at the eight "genetic centres" in the country, but the plan is to add other centres in order to gain a complete overview.

The registry is part of Belgium's national plan for rare diseases proposed by the minister of public health at the start of 2014.

The government points out that the registry is a valuable source of information not just for government authorities but also for patients and patient organizations, care providers and researchers and is used to contribute to improvements in epidemiology, care policy, quality assurance, research and administration.

Along with the basic demographic data about the patients, the registry includes the dates of the first symptoms of the rare disease (defined as the date of the first consultation with a physician for this reason), the first consultation at the specialist health care institution and when the current diagnosis was made and whether the diagnosis is provisional or definitive. It also requires the code for the disease within an existing disease classification system and information about the basis on which the diagnosis was made (e.g., based on clinical symptoms, genetic test, biochemical test, etc.).[29]

FRANCE

In June 2021, France unveiled its Health Innovation 2030 Plan, which expedites access to innovative treatments and encourages their development in the country by promoting the growth of local biotech companies and their research.

The plan allows market access immediately after approval by the French National Health Authority for all products assessed with an "Improvement in Actual Medical Benefits" for a two-year test period. The plan also calls for the French system to achieve better market access times for medicines and medical devices than the European targets.[30]

GERMANY

In Germany, normally when new treatments are approved, they are assigned a ranking from one of six levels of benefit they provide to determine their priority for pricing and reimbursement. The categories are "less additional benefit" (meaning less benefit than existing therapies), "no additional benefit," "non-quantifiable additional benefit," "minor additional benefit," "considerable additional benefit" and "major additional benefit."

However, for new rare disease treatments, the legislation specifies that the additional medical benefit has already been proven by the approval. As a result, the first two lowest categories of benefit cannot be assigned. As well, for rare disease treatments an additional benefit does not have to be proven by comparison to an appropriate comparative therapy that had been previously approved by the German regulator, as is necessary for other new treatments. [31]

ITALY

Italy has specific programs to allow prompt country-wide access to rare disease treatments thanks to a nationwide

prescription and use tracking system to monitor costs. The AIFA's (Italian Medicines Agency's) monitoring registers platform is an information technology system that allows access to treatment in a homogeneous manner throughout the country by being able to monitor the appropriateness of the use of each treatment.

The inclusion of a new medicinal product in a register takes place after the national marketing authorization is obtained, or after the authorization of a change in the treatment's indications. In some urgent cases, the registers will also allow, reimburse and monitor use of treatments prior to market authorization.

The management of the register platform is organized through a network that includes approximately 3,500 health structures, 52 regional managers, 963 health directors, 32,857 doctors and 2,318 pharmacists. Currently, 49 pharmaceutical companies have at least one monitoring register managed by the AIFA platform. Companies interact with individual pharmacies through a profile defined on the platform, providing for the fulfillment of the conditional reimbursement agreements as stipulated from the negotiations they conduct, which can include performance-based risk-sharing schemes based on patient outcomes. [32]

SPAIN (CATALONIA)

The Catalonia region of Spain has an innovative method of using registries to carefully track medication use for specific products and evaluate their use and success, and to use that data to implement risk or cost-sharing agreement with manufacturers. Since 2008, CatSalut, the Catalonia Health Authority, has run the Pharmacotherapy Harmonisation Programme.

The Pharmacotherapy Harmonisation Programme (PHP) comprises two advisory councils, one of which, the Consell Assessor de la Medicació Hospitalària (CAMH), develops technical reports on innovative medicines and recommendations for their use outside of hospitals, including for rare disease treatments. Another body is in charge of the final proposal regarding criteria for use, clinical variables and access conditions for all medicines.

To determine the conditions for reimbursement, the PHP requires recording clinical variables for the medicines used in a centralized registry linked to the billing process to ensure compliance. Data collection through this registry allows verification of treatment effectiveness, alignment with the recommendations, establishment of quality standards, benchmarking with hospitals and feedback on the decision-making process. In addition, the it identifies uncertainties and whether there is a need to negotiate a risk-sharing agreement with the manufacturer.

UNITED KINGDOM

The United Kingdom has created an early access to medicines scheme (EAMS) that aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization when there is a clear unmet medical need. Under the scheme, the Medicines and Healthcare products Regulatory Agency (MHRA) will give a scientific opinion, valid for a year and renewable, on the benefit/risk balance of the medicine, based on the data available when the EAMS submission was made.

Applying for the EAMS is voluntary and the opinion under the program does not replace the normal licensing procedures for medicines. The scientific opinion will be provided after an evaluation of whether the treatment is entitled to a promising innovative

medicine (PIM) designation and the early access to medicines scientific opinion. The PIM designation will give an indication that a product may be eligible for the EAMS based on early clinical data. The PIM designation will be issued after an MHRA scientific meeting and could be given several years before the product is licensed.[33]

UNITED STATES

The US Congress passed the Orphan Drug Act 40 years ago, in 1983. It incentivizes the development of rare disease treatments. Under the act, innovators can request orphan product designation if it meets certain criteria set by the Food and Drug Administration (FDA). Among the benefits of this designation are tax credits for qualified clinical testing in humans, waiver of the Prescription Drug User Fee (currently at almost US$3 million for a new medicine) and a potential seven years of market exclusivity after approval.

The act defines a rare disease as one that affects fewer than 200,000 people in the U.S.[34]

Importantly, the act led to the development of an industry that didn't exist before to develop such treatments, enabling the formation of many companies pursuing research into treatments for rare diseases. [35]

The Orphan Drug Act also established the Orphan Product Grants Program to provide funding for clinical investigators to develop products for rare diseases or conditions. During the past 40 years, the program has funded clinical trials that have facilitated the approval of more than 80 products. [36]

In 2002, the Rare Diseases Act passed by the US Congress created the Genetic and Rare Diseases (GARD) Information Center, a public health resource to support people living with a rare disease and their families with free access to reliable, easy to understand information, in English and Spanish. The GARD website has no advertising and GARD does not endorse or promote any companies, products or services. GARD is managed by the National Center for Advancing Translational Sciences (NCATS), a part of the National Institutes of Health and the federal government agency responsible for biomedical research. [37]

The leading rare disease patient group in the US, the National Organization for Rare Disorders (NORD), has created a network of certified centers of excellence to help patients find the best possible care and support for their disease. NORD says that each centre offers world-class doctors in all major specialties and brings together medical teams experienced in diagnosing and treating a wide array of rare diseases. In addition, researchers at each facility work with doctors and patients to find more treatments and cures for rare diseases. NORD also interconnects this network to encourage collaboration and sharing of best practices and expertise.[38]

RAREI'S THREE-POINT VISION

RAREi believes Canada has a unique opportunity to create the one of the best health systems in the world to test for, diagnose and treat rare diseases. In this context, it is pleased to provide a RAREi vision for optimizing rare disease care in Canada using key learning and successes from other countries.

The following section describes RAREi's vision for rare disease care in Canada.

VISION 1: BETTER ACCESS TO THERAPIES

This is an unprecedented and very encouraging time for the development of new treatments for rare diseases thanks to the ever-increasing understanding of the genetic underpinnings of many diseases and the development of technologies to fix the underlying genetic and other causes of many rare diseases. New treatments are saving and transforming patients' lives.

However, these new treatments and the small populations they serve must deal with a regulatory and reimbursement system created for something else entirely – medicines developed to treat common conditions affecting large populations. A key element of a comprehensive plan for helping Canadians with rare diseases must include, as has been done in other comparable countries, adapting the regulatory environment to accommodate the special circumstances of medication development and clinical testing for diseases with very small patient populations to permit swift but safe study and approval of new treatments.

Action is needed to create special systems and pathways for treatments for rare diseases at each stage of the process:

- **Regulatory system:** The federal government should implement a separate regulatory framework for rare disease treatments that includes incentives to develop and commercialize rare disease therapies in Canada, including a definition

of rare disease, an orphan product designation process, additional market exclusivity, research promotion funds, tax incentives and regulatory submission fee reductions. In cases where no approved and marketed alternative exists in Canada for rare disease patients, the SAP should remain available as a means of facilitating patients' options for accessing rare disease treatments, though reforms to its functioning are important to reduce routine reliance on it and to simplify its use by medical practitioners when it is needed.

- **Health technology assessment:** The governments that fund and direct CADTH should mandate to adopt processes, criteria and standards that are more appropriately suited for assessing rare disease treatments. Similarly, the Quebec government should do likewise for INESSS. CADTH and INESSS should both adopt specific processes, criteria and standards for rare disease treatments that help address the unique characteristics of these therapies, including specialized clinician expertise, patient values, smaller study sizes, more frequent reliance on trials other than RCTs and the higher cost of treatment per patient.
- **Product availability/reimbursement:** There is no reason why Canadian rare disease patients should wait for months or even years following regulatory approval to have access to new treatments while the HTA and reimbursement review process plays out. As in other countries, access to new treatments should be provided immediately upon regulatory approval by Health Canada. This could be achieved easily by mandating the pCPA, of which all public drug plans in Canada are members, to develop an agreement for a simple process with treatment providers that sets out the parameters and logistics for doing so.
- **Intellectual property framework:** It is crucial for developers of new treatments for rare diseases to know they can have a reasonable expectation of recovering their research investments (for both successful treatments and the inevitable research failures) by having an appropriate intellectual property (IP) framework to achieve that objective. Given the added uncertainties in the development of treatments for rare diseases and the very limited size of the markets for such treatments, the IP regime in Canada should be adapted to provide for an orphan product designation that would include added incentives for the development and commercialization of rare disease treatments in Canada. As noted above, the Orphan Drug Act in the U.S. has been very successful in incentivizing development of rare disease treatments in the US for the past 40 years. It is long overdue that Canada enact similar incentives to assist the growing product development initiatives in Canada.

VISION 2: IMPROVED CARE PATHWAYS

Canadian patients and clinicians often face great obstacles when medical symptoms and conditions do not match those that are commonly seen and treated by the health system.

It is vital that this be remedied by creating the means for health professionals to quickly access information that could help them in these situations, which would result in quicker patient referral, and faster diagnosis and subsequent treatment.

One of the challenges, of course, is the nature of rare diseases themselves and of how health care in Canada is provided. Rare diseases, by definition, affect small numbers. Health care in Canada is provided through 13 different provincial and territorial systems, serving populations ranging from 15.8 million in Ontario to 176,000 in Prince Edward Island and 41,000 in Nunavut.[39] Since there are some 7,000 rare diseases, with many affecting just dozens of patients across Canada or even less, it's not surprising that health facilities and health professionals are simply not informed or equipped enough to recognize a specific disease or know how to manage it.

It is crucial for knowledge, expertise and resources about rare diseases to be shared across provincial and territorial boundaries. What is needed is a mechanism to make that knowledge known and to make it easily available to Canadians outside the jurisdiction where it happens to exist.

This shall be accomplished by creating a formal network involving all elements of the Canadian rare disease community. In conjunction with the federal government's national Rare Disease Drug Strategy, the new network is being implemented in order to bring together all the partners in the rare disease community.

The network will serve as a cross-country forum involving multidisciplinary partners working together to address the unique challenges faced by children and adults affected by complex and rare diseases across Canada. It will connect the health care system, various academic programs of expertise and patient organizations across Canada, with the shared aim of improving access to timely and accurate diagnosis, enabling access to the best treatment options and facilitating high-quality care for people with complex and rare diseases requiring specialized expertise or resources.

Its mission and goals are to:

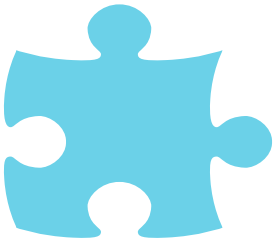
- Be inclusive of designated multi-disease programs of expertise providing comprehensive services;
- Be inclusive of disease-specific clusters or disease groupings located across several sites;
- Partner with rare disease patient organizations and include patient advocates in all working groups;

- Collaborate across programs of expertise to share best practices, training, support and new knowledge;
- Consult and support community-based institutions and service providers;
- Partner with patients and families for access to diagnosis, referral, treatment, and care;
- Participate in monitoring and evaluation based on quality standards and outcome measures.

The network's Initial activities will focus on three interconnected pillars (i.e., Precision Diagnostics and Registries, Innovative Therapies, Care, Support and Empowerment) and various platforms (e.g., data, equity, diversity and inclusion, training, knowledge mobilization).

Progress in all these areas will be vital to meeting the shared commitment to improving the health and well-being of children and families with complex and rare diseases:

The network will provide a framework for monitoring and managing safe and effective use of rare disease therapies in real-world settings. Patient data platforms will allow for collection of patient outcomes in real time and capacity for collective analysis which will help determine cost-effectiveness and demonstrate the value-based return on investment in diagnosis and treatment.



VISION 3: FOCUSED ON RESULTS FOR PATIENTS

Each stage of the rare disease system in Canada must be focused on and incentivized to provide the best possible value for patients rather than simply meet objectives defined by and meaningful to the health system itself and, in particular, its payers. That is not to say the rare disease system in Canada should have a blank cheque. Rather, it means it should be structured in a way that provides maximum value to all, including both patients and their families as well as governments and other payers.

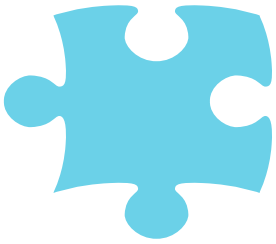
The key question in determining the state of any rare disease program should not be on what it might cost or the obstacles involved in achieving it, but rather whether or not it provides real value to both patients and the health system. If it does, then all parties involved should work together to ensure it happens. RAREi is committed to adhering to this value-based health care approach to improve care for the millions of Canadians affected by rare diseases.

One of the key roles of the proposed national rare disease network as outlined in the previous section should be to evaluate and report on not just the cost of managing rare diseases in Canada, but the resulting value – how the changes improve and extend patients' lives, make more efficient use of health care resources, stimulate the health care innovation environment in Canada and encourage investments in research and create spinoff economic activity.

Through these proposed changes and by taking a value-based health care approach, Canadians with rare diseases and their families would be provided with:

- Faster and improved access to testing and diagnosis services
- Faster and improved access to expert specialized care
- Faster and easier access to innovative therapies
- More access to ancillary products and services to improve their quality of life, and
- Unimpeded access to the best possible care anywhere in Canada without bureaucratic barriers or delays

With this approach and these proposed measures, Canada could really develop a world-class rare disease care system and become a model for other countries to potentially follow.



CONCLUSION

While this is an extremely exciting time for the rare disease community given the incredible scientific and technological advances in recent years, there is still a lot of work to be done to ensure the benefits of these new technologies reach the Canadian patients who need them.

By moving to achieve the very realistic three points of this vision, Canada could lead the way in helping overcome the challenges in accessing rare disease diagnosis, care and therapies.

But we need the final piece of the puzzle to make this a reality – the political will. RAREi hopes to work with governments, health system bodies, patient groups and everyone involved and vested in helping patients with rare diseases in Canada to achieve these positive outcomes. It is a challenge that we as a country must rise to meet.

A WORD FROM PATIENTS

What every rare disease patient wants is access to an effective therapy, often in the form of a drug. A treatment helps create a pathway for diagnosis. Unfortunately, 40 years after the 1st Orphan Drug Act, only about 5% of rare diseases has an effective drug available. And it is not for want of trying and investment. It's just very hard to discover the drugs, do the clinical trials, collect the data for approval, and then navigate the reimbursement barriers. For Canadians, the result has been fewer drugs, later entries to Canada, and slower progression to access.

The Canadian Organization for Rare Disorders (CORD), the national alliance of rare disease patients and patient groups, creates pathways between patients and researchers, between those developing the drugs and those approving them, and between the patient community and the public.

Over the years. CORD has partnered with RAREi in providing awareness, education and advocacy toward our shared commitment to achieving better outcomes for Canadian patients and families. One important outcome has been the launch of the National Rare Disease Drug Strategy. But one year later, it has not been implemented. This vision document will hopefully help advance the work at a time when the right actions could yield the greatest benefits.

EPILOGUE – FOUR REASONS WHY WE DO WHAT WE DO

Girl with deadly inherited condition is cured with gene therapy on NHS

By Andrew Gregory, *The Guardian*, United Kingdom, Feb. 15, 2023 (photo by PA, *The Guardian*)

A girl born with a rare and deadly genetic condition is expected to live a long and normal life after becoming the first person to be cured on the NHS with the help of a revolutionary gene therapy.

Teddi Shaw was diagnosed with metachromatic leukodystrophy (MLD), an inherited condition that causes catastrophic damage to the nervous system and organs. Those affected usually die young.

But the 19-month-old from Northumberland is now disease-free after being treated with the world's most expensive drug, Libmeldy. NHS England reached an agreement with its maker, Orchard Therapeutics, to offer it to patients at a significant discount from its list price of £2.8m.

In a first, a fatal enzyme deficiency is treated in the womb

By Andrew Joseph, *STAT News*, Nov. 9, 2022, about a patient treated at Children's Hospital of Eastern Ontario, Ottawa (photo by André Coutu, CHEO)

To protect this child from the same genetic disease that killed two older siblings, treating her as soon as she was born might only work so well, the doctors knew. So they dialed back the therapeutic clock, delivering the medication to her as a fetus.

Now 16 months old, Ayla appears totally healthy. She still requires weekly doses of the medication (which she receives at Ottawa's Children's Hospital of Eastern Ontario), an enzyme that she can't produce on her own, but she has no symptoms of the condition she inherited, the most serious form of the rare Pompe disease. Her heart is strong, and she started walking at a typical 11 months old.

Ayla's case, described Wednesday in the *New England Journal of Medicine*, was the first in which doctors provided this type of treatment — called enzyme replacement therapy, or ERT — in utero. To help a family the disease had already marked with tragedy, experts at multiple institutions across borders had to overcome both a narrow window to provide care as well as Covid-19 travel barriers.

A devastating skin condition could soon get its first medication, as the frontiers of gene therapy expand

By Andrew Joseph, STAT News, April 3, 2023 (photo by Constanza Nevia for STAT News)

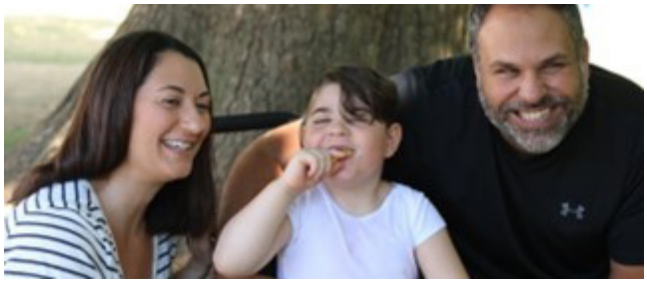
Wounds have been a constant fact of Aaron Owens' life. His skin is so fragile that friction that would be trivial to others — rolling over in bed, weight shifting against the seat as the car turns — could scrape off his tissue. He didn't like being in public sometimes because people would stare at the boy covered in bandages.

When he enrolled in a clinical trial a few years ago, the teenager didn't know which wound on his body was treated with the experimental medication, and which was dosed with a placebo. This trial wasn't like so many others where some enrollees get the drug in question and others get a sham dose. Rather, Owens received both, but on different wounds.

Soon, though, Owens noticed that portions of skin in some areas started to heal, and heal faster and stronger than he had experienced in his lifetime contending with these wounds. It was a clue that, maybe, the medication was working.

Owens, an 18-year-old high school student, has epidermolysis bullosa, or EB, a genetic condition that causes the skin to be so exquisitely delicate that it's likened to a butterfly wing. In severe cases, even slight touches lead to blisters that can form persistent wounds. The accumulated scarring can fuse fingers and toes together. People live in constant pain.

Postscript: The Food and Drug Administration approved the new treatment for use in the U.S. on May 19, 2023.



Toronto boy whose parents raised $3M to treat his rare genetic disorder starts clinical trial

By Ioanna Roumeliotis and Perlita Stroh, *CBC News*, August 16, 2022 (photo by Ousama Farag, CBC)

After his parents desperately raised $3 million over three years trying to find a cure for their son's rare genetic disease, Michael Pirovolakis is one step closer to possible recovery.

Michael, 4, is the only child in Canada diagnosed with spastic paraplegia 50 (SPG50), a slowly progressing neurodegenerative disorder that generally presents with global developmental delay resulting in cognitive impairment and eventual paralysis.

This past March, doctors at SickKids Hospital in Toronto injected a normal version of the gene he's missing into Michael's spinal fluid to be delivered to his brain. The one-dose therapy is part of a ground-breaking clinical trial where Michael is the only participant.

And already, Georgia and Terry Pirovolakis, Michael's parents, say they are seeing some signs of hope.

APPENDIX

About RAREi

RAREi is a network of 18 Canadian biopharmaceutical companies committed to improving the lives of Canadians with rare diseases by researching, developing and commercializing rare disease treatments. The member companies of RAREi are:

Alexion Canada
Amicus Therapeutics
Argenx Canada
Astellas Canada
Biogen Canada
Biomarin Pharmaceutical
Boehringer Ingelheim Canada
GlaxoSmithKline Canada
Horizon Therapeutics
Ipsen Canada
Janssen Canada
Mitsubishi Tanabe Pharma Canada
Recordati Rare Diseases
Sanofi Canada
Sobi Canada
Takeda Canada
Ultragenyx Pharmaceutical Canada
Vertex Canada

About the Canadian Organization for Rare Disorders

The Canadian Organization for Rare Disorders (CORD) is Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research, diagnosis, treatment and services for all rare disorders in Canada. For more information, visit www.raredisorders.ca

Selected international rare disease organizations

Rare Diseases International: https://www.rarediseasesinternational.org/

Australia: Rare Voices Australia, https://rarevoices.org.au/

Belgium: Rare Disorders Belgium, https://rd-b.be/en/

Europe: European Organisation for Rare Diseases (EURODIS), https://www.eurordis.org/

France: Foundation for Rare Diseases, https://fondation-maladiesrares.org/en/

Italy: Italian National Association of People with Rheumatological and Rare Diseases (APMARR), https://asif.info/country/italy-apmarr/

Germany: National Action League for People with Rare Diseases, https://www.namse.de/english

New Zealand: Rare Disorders NZ, https://www.raredisorders.org.nz/

Spain: Spanish Federation of Rare Diseases (FEDER), https://www.enfermedades-raras.org/

United Kingdom: Rare Disease UK, https://www.raredisease.org.uk/

United States: National Organization for Rare Disorders (NORD), https://rarediseases.org/

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