Closing the Gap By Understanding the Burden of Rare Disease in Canada

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Learning Objectives

Discuss the challenges in conducting rare disease research in Canada

To discuss how real world data and real world evidence offer a unique opportunity to evaluate the impact of rare disease on the healthcare system.

A research program example and lessons **learned** to date will **be** shared

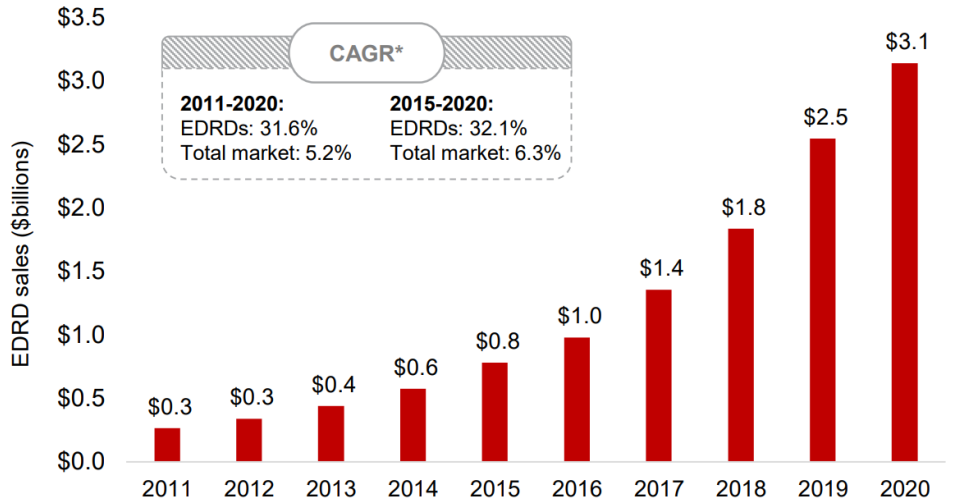

clideo.com

Rare Disease in Canada

- 7,000 rare genetic diseases in Canada that impact more than one million Canadians and their families
- 2/3 of these diseases cause significant disability
- 3/4 affect children
- More than 1/2 lead to early death
- More than 1/3 of these diseases remain unsolved (their genetic cause is unknown).

Drugs for Rare Diseases in Canada

- At present only a small number of rare diseases have treatments
- EDRD= expensive drugs for rare disease
- EDRD sales have grown at an average annual rate of nearly 32% since 2011
- Information gaps related to these drugs and their high treatment cost is a challenge for decision makers in Canada



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Annual growth rate	-	28.1%	29.5%	30.6%	36.1%	25.3%	38.5%	35.3%	38.8%	23.2%
Share of Canadian pharmaceutical market	1.4%	1.7%	2.2%	2.8%	3.5%	4.2%	5.4%	7.0%	9.1%	10.4%
Share of patented medicine sales	2.2%	2.8%	3.4%	4.0%	5.2%	6.3%	7.8%	11.7%	15.1%	17.4%

Expensive Drugs for Rare Diseases. Canadian Trends and International Comparisons, 2011-2020

National Drug Strategy for Rare Disease

Seek national consistency in coverage for drugs for rare diseases

Support patient outcomes and system sustainability

Collect and Use Real-World Evidence

Invest in Innovation

Leveraging Real World Evidence in Regulatory Submissions of Medical Devices | FDA

Real World Data

Data that is collected in the context of the routine delivery of care as opposed to data collected within a clinical trial where, study design controls variability in ways not representative of real-world care and outcomes

Real World Data

Clinical Data	Patient Generated Data	Cost and Utilization Data	Government Data Sources
• Demographics, history, comorbidities, procedures, treatment hx and outcomes	• Provide insight directly from the patient • Help understand what happens outside of clinic visits/ procedures/ admissions	• Health administrative databases • Prescribing patterns, population coverage and how using the healthcare system	• Info about the needs of the population they service

Real World Evidence

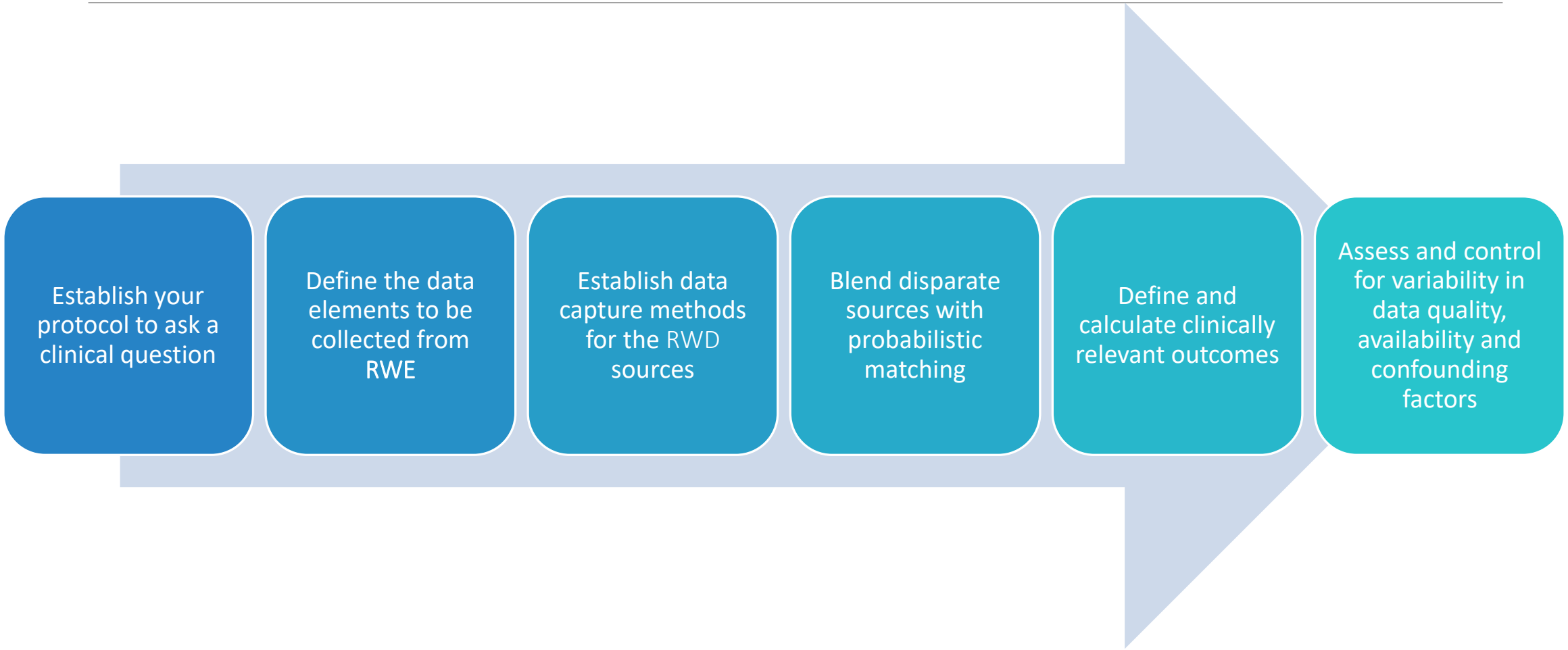
The clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data

Why do we need it?

To bridge the gap between research (what we learn) and everyday practice (what we do) in healthcare, and it creates a difference between what is expected to happen and what *really* happens.

Provide regulatory bodies with data outside of 'clinical trials' to expand access to disease modifying therapies

Real World Evidence- How Do We Use It?



https://www.arbormetrix.com/blog/9-ways-real-world-evidence-is-changing-healthcare

Real World Data

Clinical Data

- Demographics, history, comorbidities, procedures, treatment hx and outcomes

Patient Generated Data

- Provide insight directly from the patient
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Cost and Utilization Data

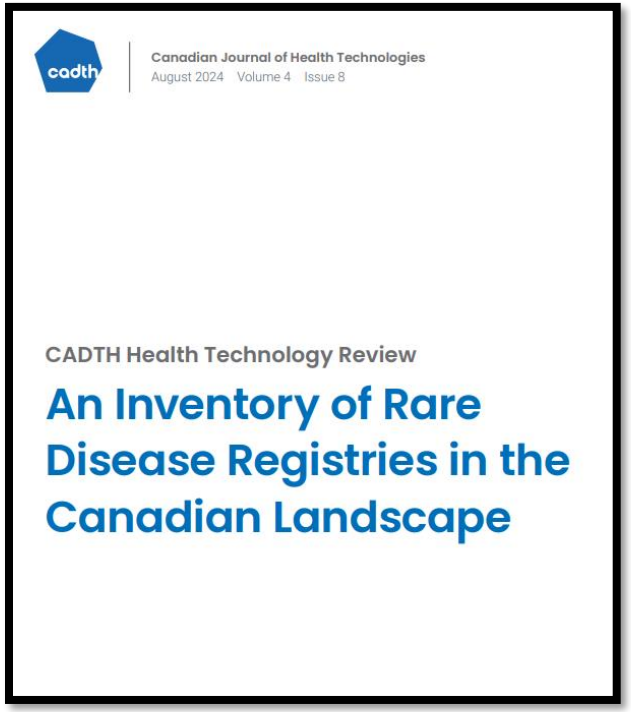
- Health administrative databases
- Prescribing patterns, population coverage and how using the healthcare system

Government Data Sources

- Info about the needs of the population they service

Patient Registries

- Registries are a rich source of real-world data
- 66 RDRs in Canada and 82 international RDRs
- Demographics, history, comorbidities, procedures, treatment history including disease modifying therapies and outcomes
- Diagnosis
- Limitations
  - Completeness of the data
  - Patient consent to link to health administrative databases

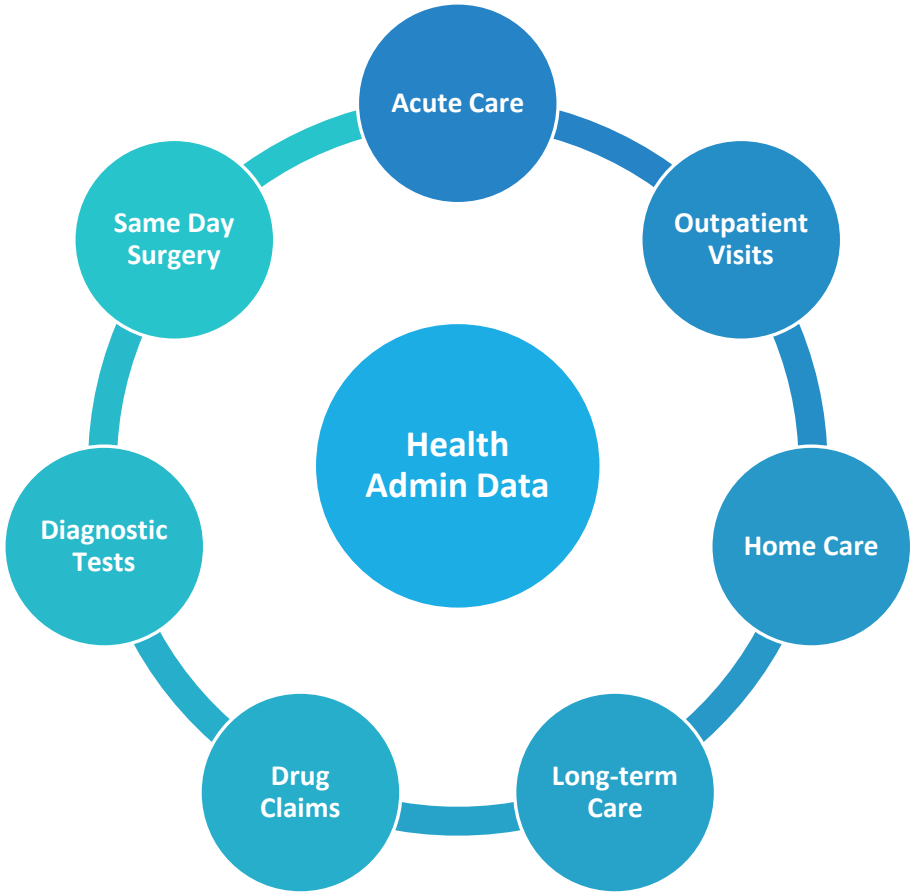


Health Administrative Data

- Health care administrative data are generated at every encounter with the health care system
- Health care utilization data, administrative health care billing records, administrative claims data, or simply claims data are synonymous with health care administrative data
- Data collected for administrative or billing purposes, yet may be leveraged to study health care delivery, benefits, harms, and costs.

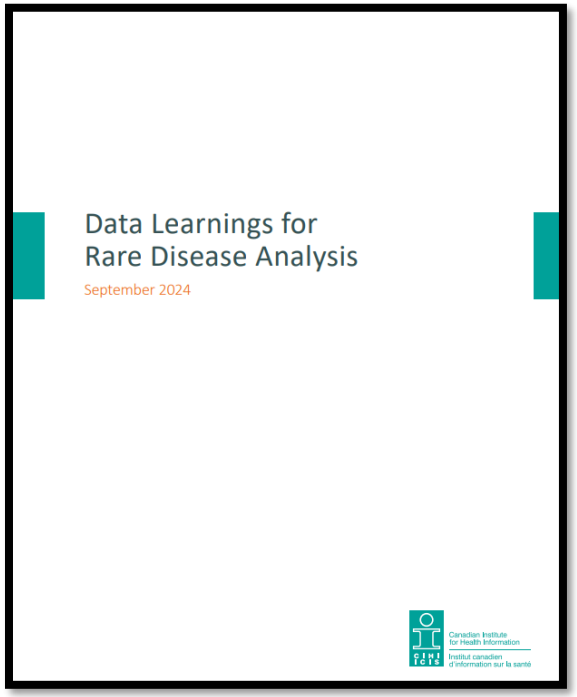
Cadarette et al Can J Hosp Pharm 2015

Health Administrative Data



- In Canada we have national and provincial data holdings
- Canadian Institute of Health Information (national)
- Provincial health administrative databases
- Significant variability in data coverage

How Patients Interact with the Health care System



Health care setting and coverage	Overview
Acute care and emergency department • Databases – DAD, NACRS* • Coverage – Acute care: Pan-Canadian – Emergency department: Selected provinces/territories	Acute care (hospital inpatient) and emergency department use can represent necessary hospital treatment for severe episodes of illness and poor outcomes (e.g., severe infections, end of life). These databases may capture only a subset of the rare disease population, such as those who are the most ill, and would not be representative of the broader patient population due to most care occurring in the outpatient setting.
Outpatient clinics • Database – NACRS* • Coverage – Limited	Outpatient clinic visits in the hospital (when the patient is not admitted) can be a major source of care for those with rare diseases. These health care encounters could provide insights about routine care and health outcomes for patients with rare diseases. CIHI receives limited clinic data.
Home care • Databases – HCRS, IRRS-HC • Coverage – Selected provinces/territories	Publicly funded home care can support some people with rare diseases living in their own home or other supportive living environments. CIHI captures this data, which may provide insights about the specialized care needs of, health conditions of and clinical outcomes for people living with rare diseases.
Long-term care • Databases – CCRS, IRRS-LTCF • Coverage – Selected provinces/territories	In the community, it can be difficult to manage the care of those with rare diseases even with the support of home care services, and some patients move into more formal care settings such as long-term care. Long-term care data can provide information about care provision and health outcomes for those living with rare diseases in long-term care that is not captured in other settings.
Primary care • Database – PLPB Repository • Coverage – Selected provinces/territories†	CIHI's Patient-Level Physician Billing (PLPB) data can provide insights on the care provided to patients with rare diseases in the community and in clinics, based on physician services. Some clinics may have physicians on alternative payment plans (such as a salary), and if those physicians do not shadow bill for services delivered, those services are not captured in the data.
Pharmaceutical care • Database – NPDUIS • Coverage – Public claims: All provinces and 1 territory – Private claims: 3 provinces	NPDUIS contains claims-level prescription drug data from most public drug plans and some private plans filled through community pharmacies. Data on prescription drugs dispensed to patients can provide information about disease treatments, symptom management, complications and outcomes; in some cases, it can enable identification of patients with rare diseases through disease-specific treatments.

Variable Data Holdings Across the Provinces

Data Holdings	British Columbia	Alberta	Ontario	Quebec	New Brunswick	CIHI
Hospitalizations	Available 95% of pop'n					
Healthcare Clinic	No Data					
Emergency Room visits	Available <95% of pop'n					
Physician Billing Data						
Prescribed Medication						
Homecare Services						
Chronic Care						
Vital Statistics Data						
Primary Care/ Family Doctor	Planned					
Laboratory Test Results						
Area-level social indicators						
Immigration						

Table 1. Description of Five Common Administrative Databases in Ontario

Database	Description	Key Variables
Registered Persons Database (RPDB)	Enrolment data: Includes data on all persons enrolled in the Ontario provincial health care program and a unique encrypted patient identifier that is used for record linkage across all databases	Patient ID Date of birth Date of death Postal code

Ontario Drug Benefit (ODB) Claims	Pharmacy data: Captures medications dispensed and services billed through the ODB Program
	• Drugs listed on the ODB formulary for residents:
	  • ≥ 65 years of age
	  • younger residents on social assistance*
	• Drugs not listed on formulary but possibly funded through the Exceptional Access Program or Special Access Programme if certain criteria are met
	• Community pharmacy services (influenza vaccinations, MedsCheck, pharmaceutical opinions, smoking cessation)
		Patient ID
		Pharmacy ID
		Prescriber ID
		Date of service
		Days supplied
		Drug ID number
		Dosage form and strength
		Quantity dispensed

Ontario Health Insurance Plan (OHIP) Claims	Physician services: Captured using OHIP codes • Diagnoses (e.g., reason for office visits and diagnoses made) • Procedures (e.g., laboratory and diagnostic tests, vaccinations)	Patient ID Physician ID Date of service Diagnoses Procedures
Discharge Abstract Database (DAD)	Hospital inpatient data: Detailed data relating to hospital admissions • Diagnoses (differentiating between the most responsible diagnosis and other diagnoses) • Procedures and interventions (e.g., surgery codes)	Patient ID Physician ID Hospital (facility) ID Date of admission Date of discharge Diagnoses Length of stay Procedures
National Ambulatory Care Reporting System (NACRS)	Hospital outpatient data: Detailed data for day surgeries and emergency department services	Patient ID Physician ID Hospital (facility) ID Date of service Diagnoses Procedures

Cadarette et al Can J Hosp Pharm 2015

Identifying Patients with Rare Disease In Health Administrative Databases

Identification via diagnosis information (ICD-10)

Identification via prescribed drug

Proxy method

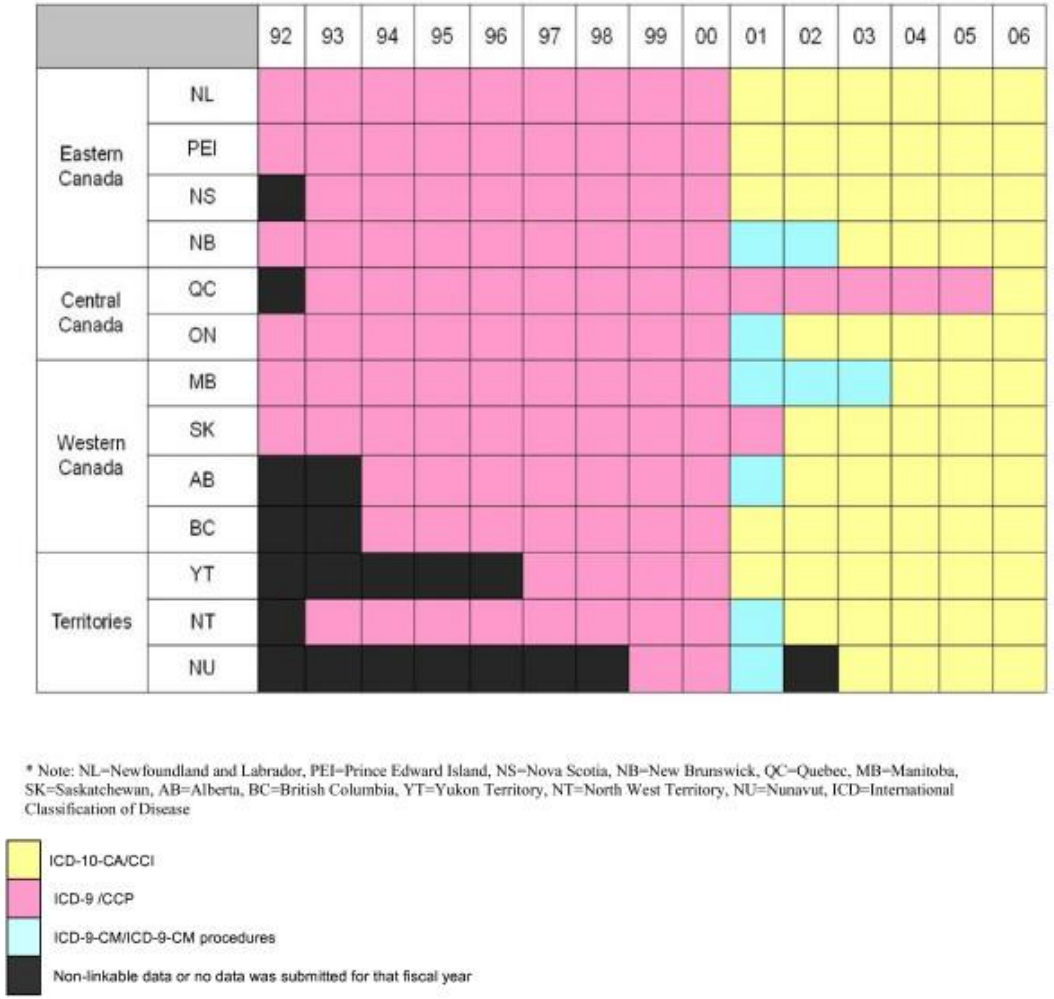
Case Example: Duchenne Muscular Dystrophy

- In the ICD-CA classification, DMD grouped with other muscular dystrophies so you can’ t use ICD-10 codes to identify patients
- There is also not a specific drug treatment available only for DMD
- To date no validated algorithm to identify DMD patient

Disease Characteristics and Health Administrative Data Analysis

- **Small patient numbers**
  - often need large look back cohorts
  - challenge is may need to go back to when ICD-9 codes used
  - increasing complexity and risk of misdiagnosis or overdiagnosis
- **Disease Onset and progression**
  - first doctor visit or first hospitalization with the diagnosis code
- **Mortality**
  - Captured if death occurs in hospital or long-term care

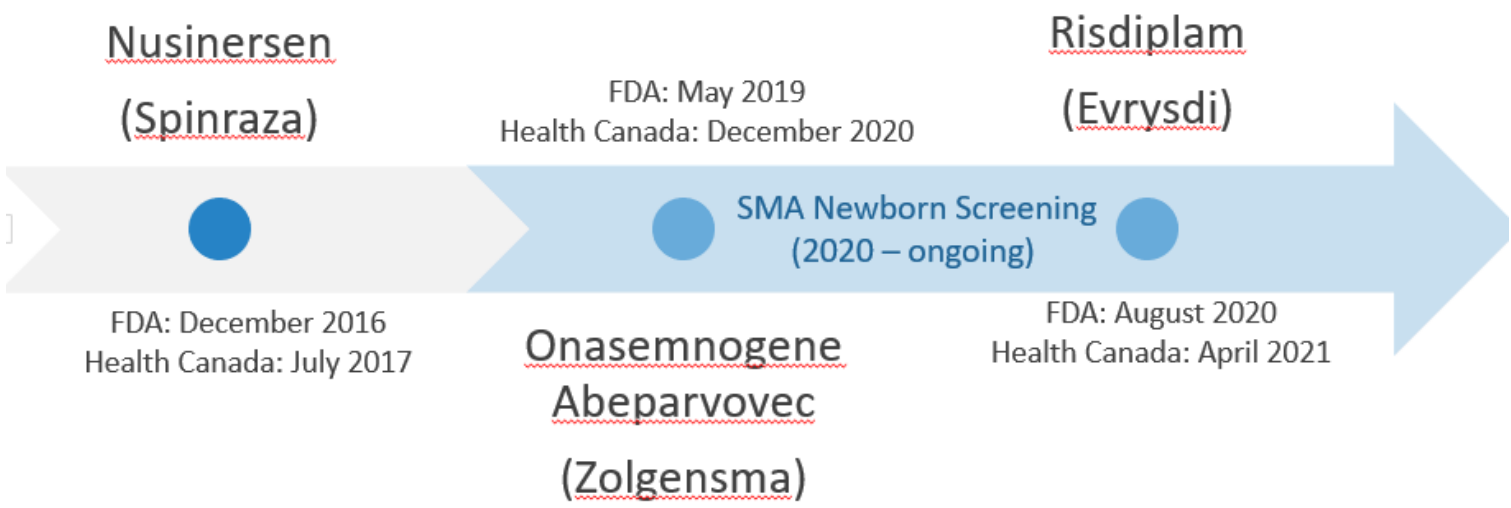
International Classification of Disease Coding Classes of Canadian Provinces and Territories, Fiscal Years 1992 to 2006



* Note: NL=Newfoundland and Labrador, PEI=Prince Edward Island, NS=Nova Scotia, NB=New Brunswick, QC=Quebec, MB=Manitoba, SK=Saskatchewan, AB=Alberta, BC=British Columbia, YT=Yukon Territory, NT=North West Territory, NU=Nunavut, ICD=International Classification of Disease

Walker et al. BMC Health Services Research 2012

Case Example: Spinal Muscular Atrophy



CHALLENGES

- Small numbers
- Several versions of ICD classification system needed
- DMT prescribed via various drug plans that will not always appear in health admin databases

Initiatives for Improved Analysis for Rare Disease at CIHI

- ICD-11 codes: will identify 5500/ 6000 rare diseases as compared to only 8% currently identified with ICD-10
- Consolidate Data into a Pan Canadian Prescription drug information system (5 year plan)
- Collaborate with rare disease registries and newborn screening programs
- Improve the coverage of data in outpatient healthcare settings: outpatient clinics and primary care

National Drug Strategy for Rare Disease

Seek national consistency in coverage for drugs for rare diseases

Support patient outcomes and system sustainability

Collect and Use Real-World Evidence

Invest in Innovation

CIHR Rare Disease Initiative

Real-World Evidence for Canadian Neuromuscular Disease: Establishing a Framework for National Integration of Patient Reported Outcomes, Clinical Registry Data, Healthcare Utilization and Healthcare Associated Costs

Thank you to Our Team and Funders

CNDR.ORG
Canadian Neuromuscular Disease Registry

Co-PI's: Victoria Hodgkinson, Hanns Lochmuller, Eyal Cohen, Gordon Jewett and Homira Osman





CIHR IRSC

MUSCULAR DYSTROPHY CANADA
DYSTROPHIE MUSCULAIRE CANADA

cure SMA

DEFEAT DUCHENNE CANADA

NMD4C

Thank you to Our Team and Funders

- Steering Committee: Victoria Hodgkinson, Hanns Lochmuller, Eyal Cohen, Gordon Jewett and Homira Osman
- Co-Investigators: CNDR Co-Investigators, NMD4C Members, Health Service Researchers and Economists
- Patient Partners
- Non-Profit Partners: MD Canada, Defeat Duchenne Canada and Cure SMA Canada

Study Aims

Aim 1: To understand the burden of NMD in the Canadian healthcare system including the prevalence, healthcare utilization, direct costs and health inequity

Aim 2: Establish a platform for real-world evidence generation for NMD that can be used as a model for rare disease

Project Objectives: *To Determine*

- Disease specific healthcare utilization nationally and provincially

Healthcare Utilization

- Disease specific prevalence nationally and provincially

Disease Prevalence

- Disease-specific costs and variation in costs between Ontario and Alberta

Disease Specific Costs

- Healthcare utilization, costs and prevalence of NMD disease by health equity stratifiers

Health equity

- Disease specific mortality

Mortality

- Sensitivity of ICD-10 codes at ascertaining NMD diagnosis vs CNDR

ICD-10 Codes

- Patient and family HRQoL

HRQoL

Part 1: Data Linkage for a Retrospective Cohort

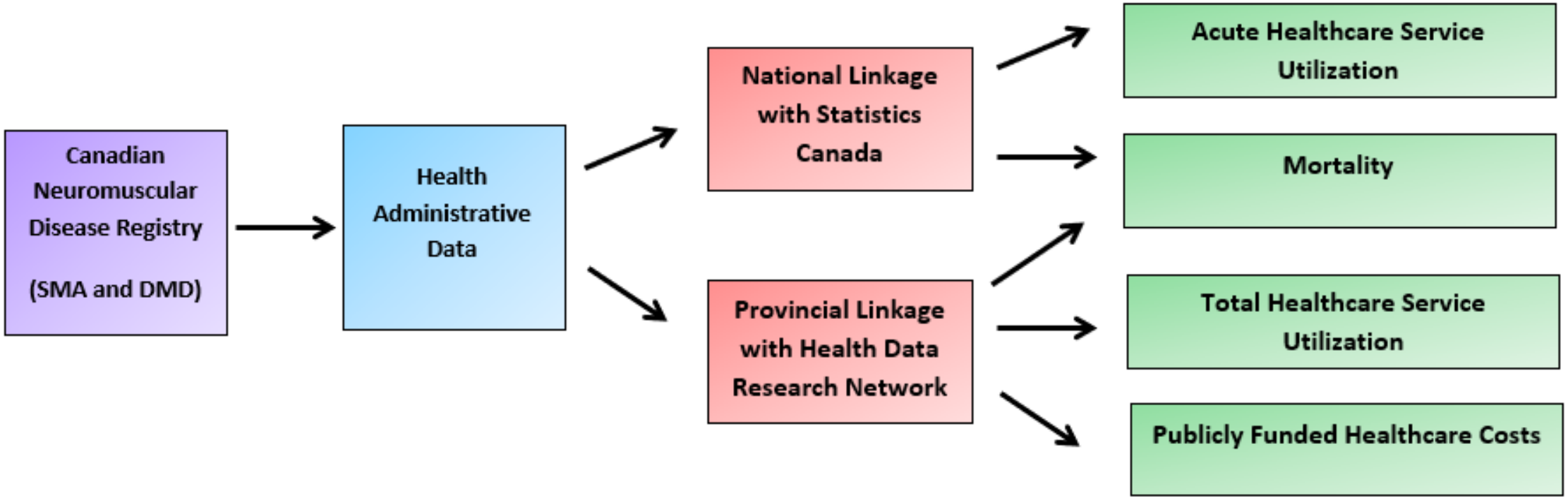


Figure 1: Aim 1 Study Overview

National Linkage with Statistics Canada

- Linking nationally enables reporting on unique socioeconomic and financial data holdings not available in provincial databases

(CIHI, Social Data Linkage Environment, Canadian Vital Statistics, T1 Family Tax Files and Longitudinal Immigration database)

- Patient prevalence in each province may be low in certain provinces →→ national linkage will enable more fulsome reporting of healthcare service utilization

Statistics Canada Statistique Canada

Part 1: Data Linkage for the Retrospective Cohort

- 5 provinces will have health service utilization
- ***Ontario and Alberta will have health service utilization associated cost analysis***
- In Ontario, will also do ICD-10 code validation against registry diagnosis for SMA and DMD

Why These 5 Provinces?

- ✓ Representation across the country
- ✓ Sufficient provincial health administrative infrastructure

Réseau de recherche sur les données de santé du Canada

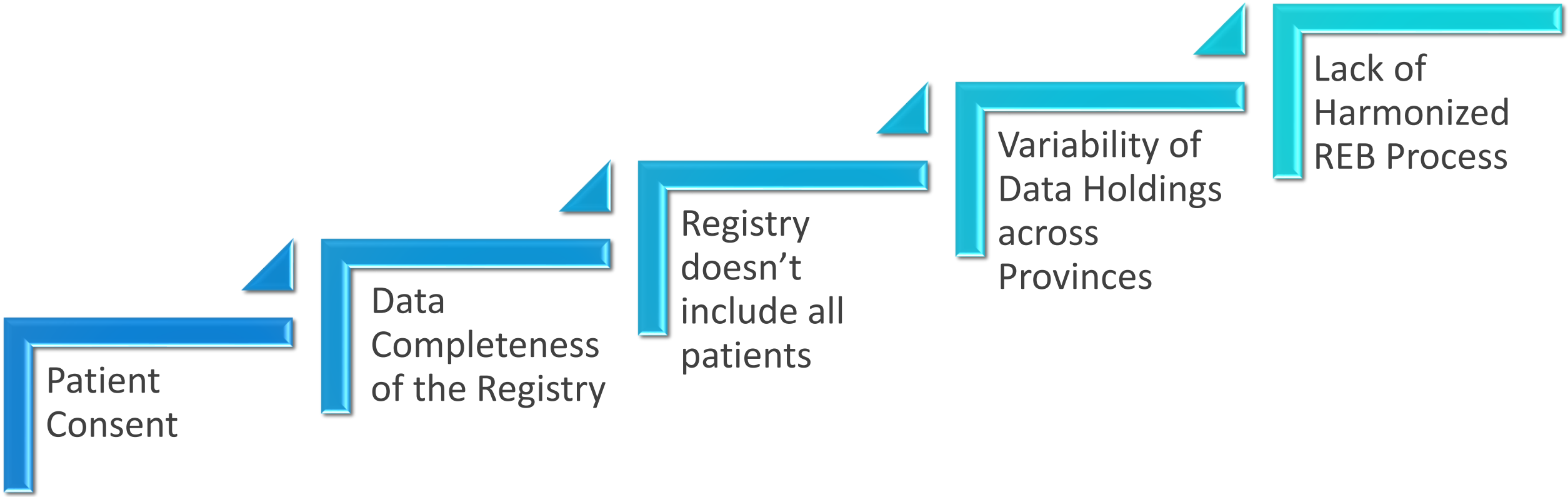
Health Data Research Network Canada

The Canadian Neuromuscular Disease Registry

- CNDR and its network of investigators is a global model for rare disease registries
- Since its inception in 2010, it has led to the recruitment of 5,000+ individuals with various NMDs
- And a huge opportunity to overcome the barriers of evaluating the impact of NMD on the patient and family and healthcare system using health administrative data alone

Registry overcomes hurdles of patient identification by diagnosis, disease diagnosis date and symptom onset, disease modifying therapy start and end dates

Anticipated Challenges



Patient Consent

- Current consent to CNDR does NOT include health administrative database linkage
- We will attempt to obtain consent for these 900 patients but waiver of consent if
  - 1) cannot be reached
  - 2) deceased

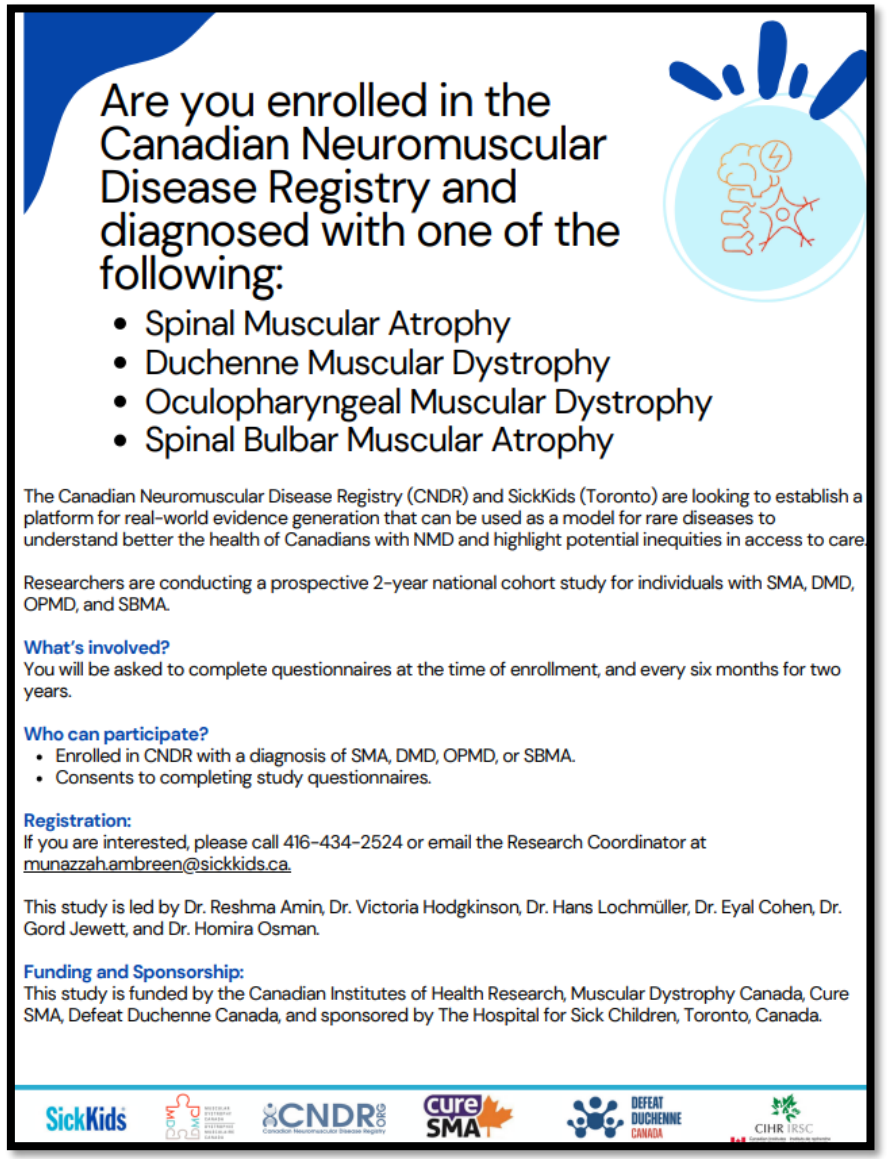
Data Completeness of the Registry

- CNDR Data Elements to link for SMA
  - Demographics: DOB (for linkage, and age); sex
  - Diagn
  - Chara
  - Inter ve ventilation use; tracheostomy; scoliosis surgery
  - DMT use and type: DMT start/stop
  - Outcomes: death; (interventions above); motor scales; probably not PRO's (limited and not standardized)

Ongoing Financial Investment in Registries

CNDR doesn't include all SMA and DMD Patients

- Plan to actively increase enrollment
- Website link to study for Cure SMA, Defeat Duchenne Canada and MD Canada
- Email blast with research flyer by three non-profits
- CNDR investigators involved



Are you enrolled in the Canadian Neuromuscular Disease Registry and diagnosed with one of the following:

- Spinal Muscular Atrophy
- Duchenne Muscular Dystrophy
- Oculopharyngeal Muscular Dystrophy
- Spinal Bulbar Muscular Atrophy

The Canadian Neuromuscular Disease Registry (CNDR) and SickKids (Toronto) are looking to establish a platform for real-world evidence generation that can be used as a model for rare diseases to understand better the health of Canadians with NMD and highlight potential inequities in access to care.

Researchers are conducting a prospective 2-year national cohort study for individuals with SMA, DMD, OPMD, and SBMA.

What's involved?
You will be asked to complete questionnaires at the time of enrollment, and every six months for two years.

Who can participate?
- Enrolled in CNDR with a diagnosis of SMA, DMD, OPMD, or SBMA.
- Consents to completing study questionnaires.

Registration:
If you are interested, please call 416-434-2524 or email the Research Coordinator at munazzah.ambreen@sickkids.ca.

This study is led by Dr. Reshma Amin, Dr. Victoria Hodgkinson, Dr. Hans Lochmüller, Dr. Eyal Cohen, Dr. Gord Jewett, and Dr. Homira Osman.

Funding and Sponsorship:
This study is funded by the Canadian Institutes of Health Research, Muscular Dystrophy Canada, Cure SMA, Defeat Duchenne Canada, and sponsored by The Hospital for Sick Children, Toronto, Canada.

Lack of a Harmonized REB Across Provincial Health Administrative Databases

- Conducting identical analysis pending data element availability across all five provinces (BC, Alberta, Ontario, Quebec and New Brunswick)
- We need to submit five separate REBs to the provincial health administrative databases
- No harmonized/ synergistic process
- In addition to separate ethics approvals, also need separate data sharing agreements
- Out of scope for the Health Data Research Network

Barrier to conducting multi-jurisdictional research

Part 2: Establishing a Data Platform for Real World Evidence

Part 2: Establishing a Data Platform for RWE

- 4 prospective, 2-year national cohort studies
- Spinal Muscular Atrophy, Duchenne Muscular Dystrophy, Spinal Bulbar Muscular Atrophy and Oculopharyngeal Muscular Dystrophy

Important Cohorts for Canadians with NMD

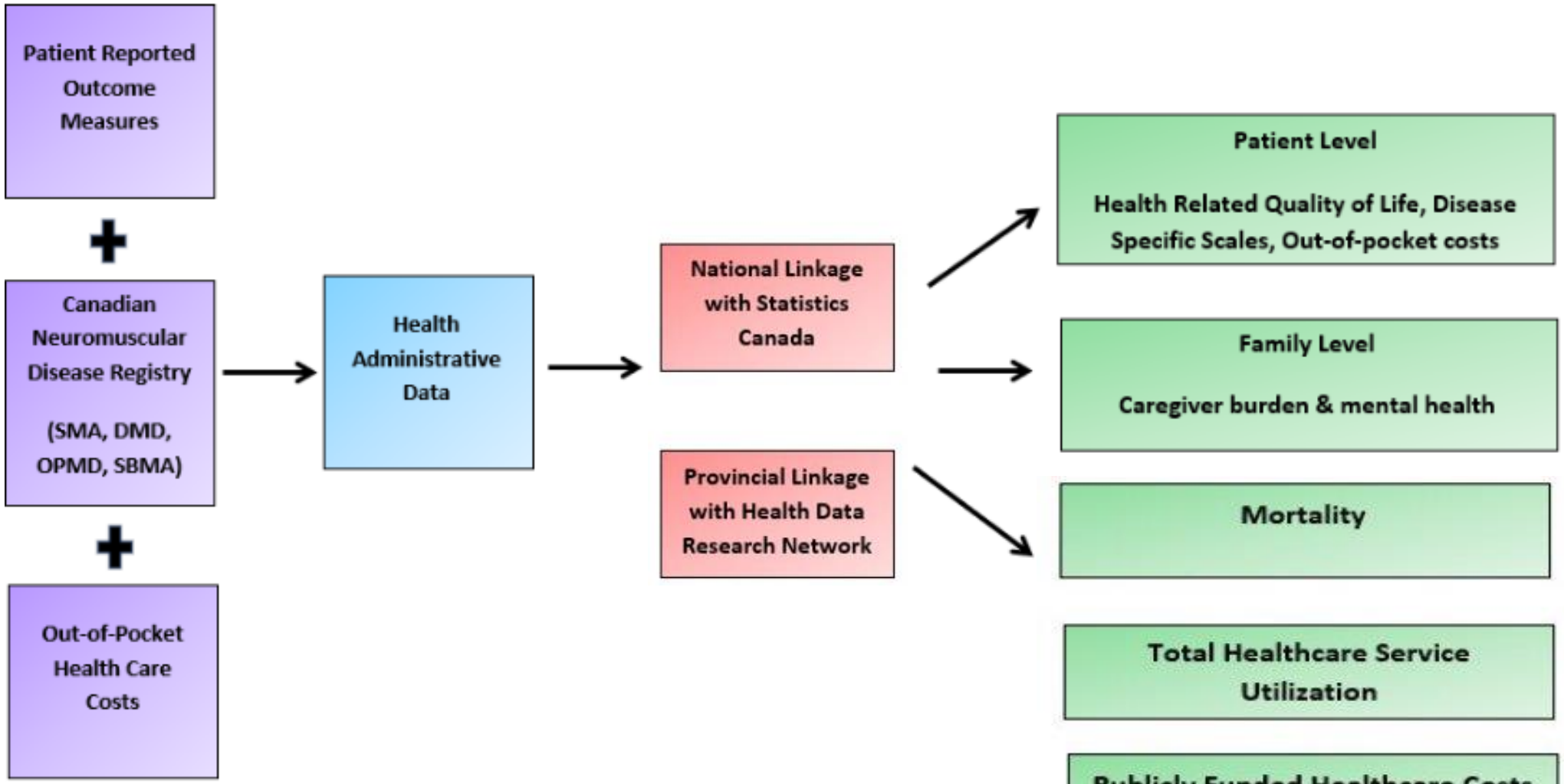


Figure 2: Aim 2 Study Overview

Part 2: Establishing a Data Platform for RWE

- Data Collected Every 6 Months
  - Registry Data (SBMA and OPMD 2 new registries being developed)
  - Prospectively collected patient reported outcome measures (PROMs): disease specific and disease generic
  - Prospectively collected out of pocket costs
  - Be able to again link to health administrative databases

Part 2: Establishing a Data Platform for RWE

- ***Patient Reported Outcome Measures***
  - Disease Specific Questionnaires
  - Disease Generic Questionnaires
    - Utility measure for economic analysis
    - HRQoL
    - Caregiver Burden and Parental Stress
    - Mental Health
    - Direct Cost tool

Indigenous Patient Engagement Plan

- Committed to ensuring research is conducted in a way that is culturally sensitive and respects Indigenous data sovereignty
- Our team (King, King, Schellenberg, Pfeffer) has engaged with Indigenous people affected by SBMA since 2020




PATIENT ENGAGEMENT

PATIENT RECRUITMENT

DATA MANAGEMENT

Research with the Indigenous Population

Research Program Anticipated Impact

Framework for rare disease linkage studies

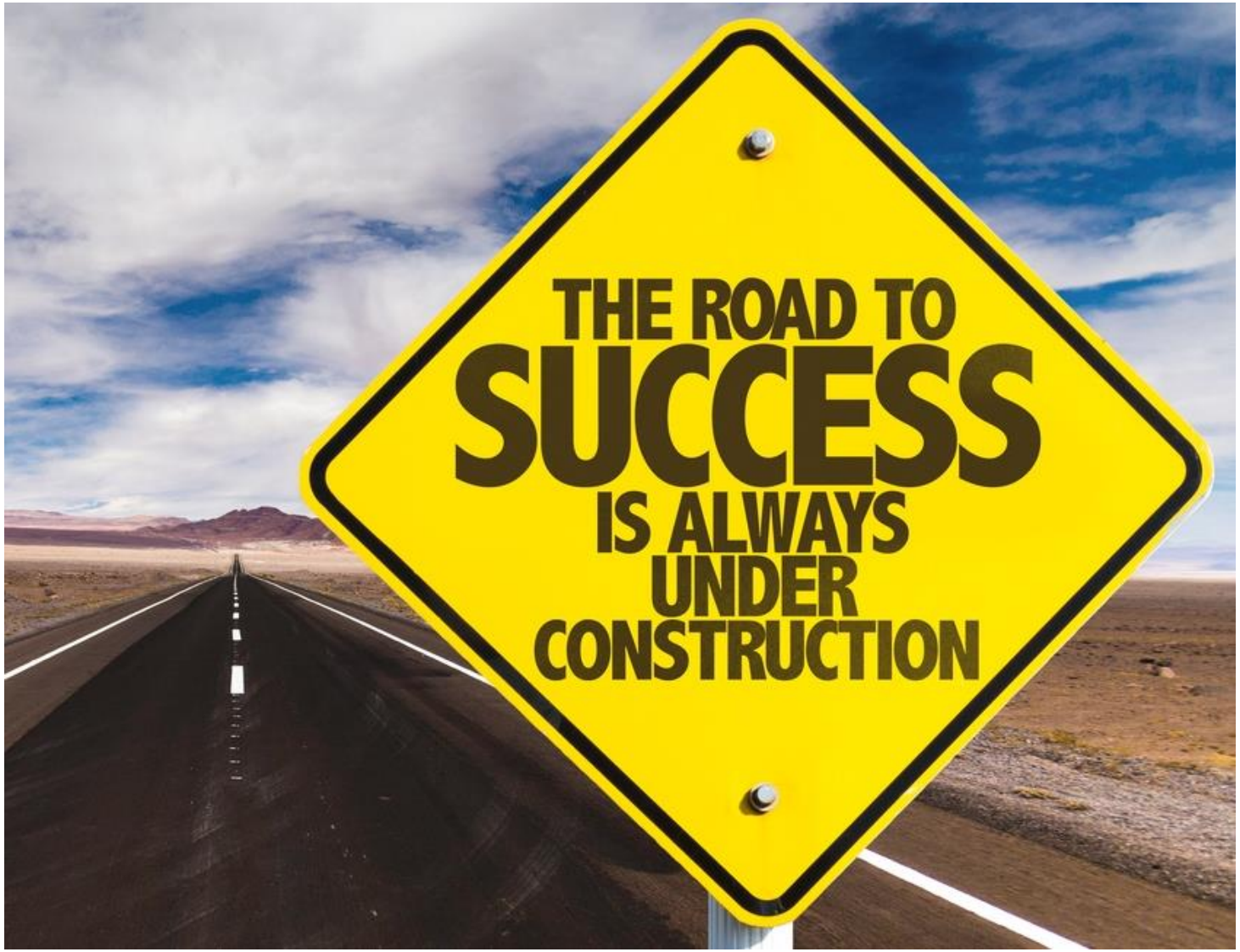
Validating ICD-10 codes and future ICD-11 codes

Inform health system decision makers on the variability in NMD disease burden

Build collaborative relationships with health administrative researchers in other provinces

Establish a platform for future cost-effectiveness studies of disease modifying therapies

An exemplar for other rare diseases to build RWE research programs



Summary

- The future for rare disease in Canada is bright: science, infrastructure and government investment
- Registries and health administrative databases are rich sources of RWD but challenges with their use and need for investment
- Our hope is for our planned program of research in neuromuscular disease to be an exemplar for other rare diseases
- Challenges and lessons learned along the way can help other investigators embarking on research platforms in other rare diseases

THANK YOU

CARE4RARE Canada