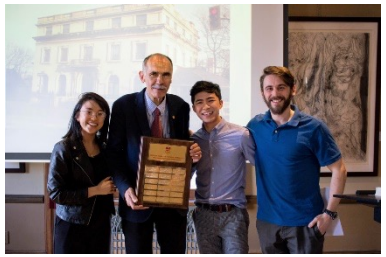
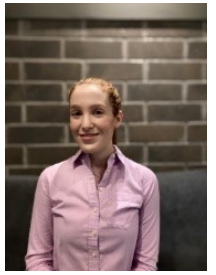
CANADIAN NETWORK FOR ADVANCED INTERDISCIPLINARY METHODS FOR COMPARATIVE EFFECTIVENESS RESEARCH

CAN-AIM

http://canaim.ca/

National research team funded by the Drug Safety and Effectiveness Network through a partnership between CIHR and Health Canada.



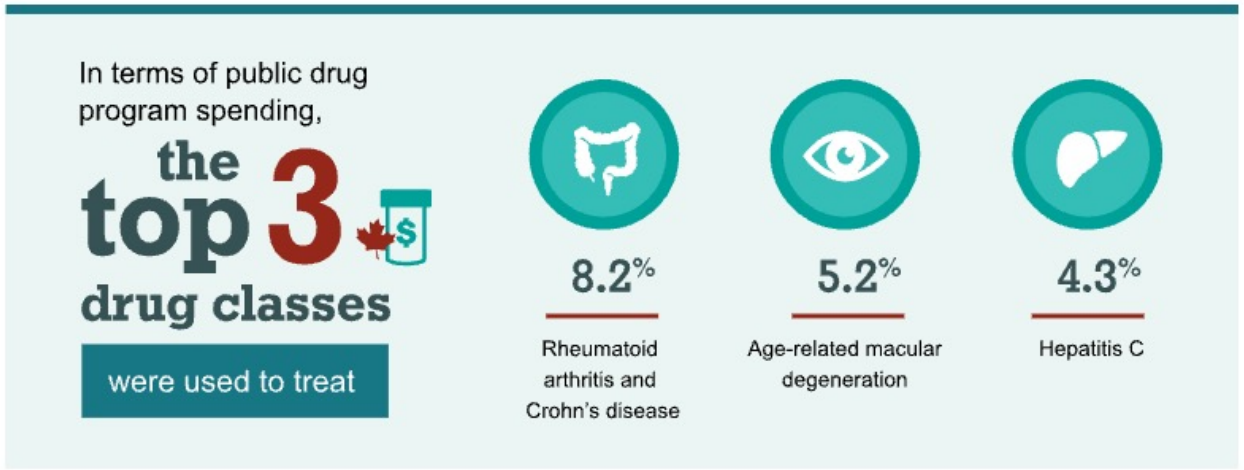


What questions will we answer today?

- Why study drug safety and effectiveness?
- What is DSEN?
- Who is CANAIM?
- How is CanPath helping provide answers for regulators regarding optimizing medication-related outcomes in Canada?
- What challenges do we face when using CanPath and other secondary data sources, to study drug safety and effectivenesss
  - Drug exposure: Getting it right
  - Examples from real projects

Why study drug safety and effectiveness?

- Public drug program spending
  - >$15 billion in 2019 (cihi.ca)



- Each **200,000 severe adverse reactions** in Canada
  - 10,000 to 22,000 Canadian deaths
  - Costs to Canadian healthcare system up to $17.7 billion.
- All are affected by drug safety and effectiveness at some point in our lives

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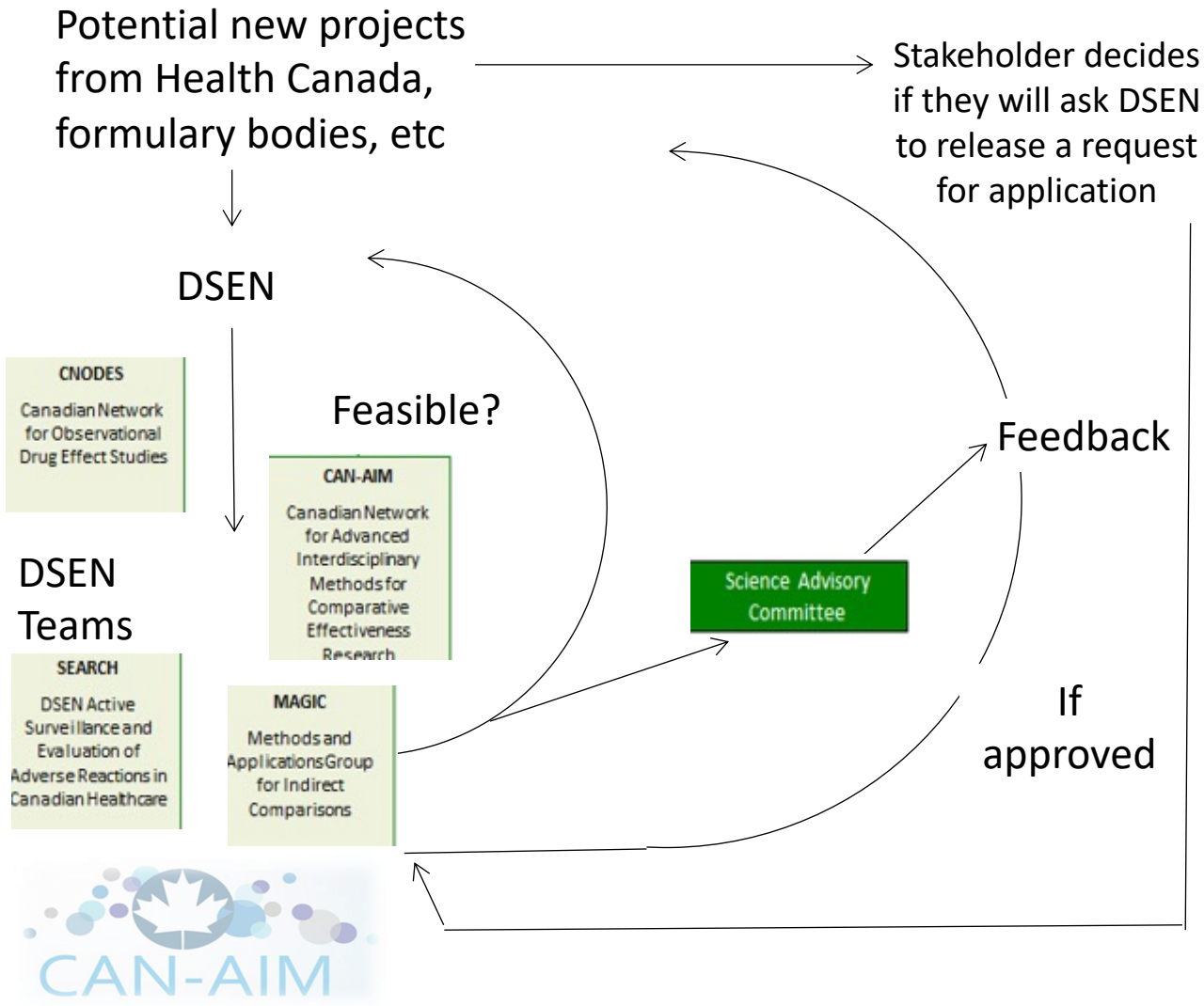
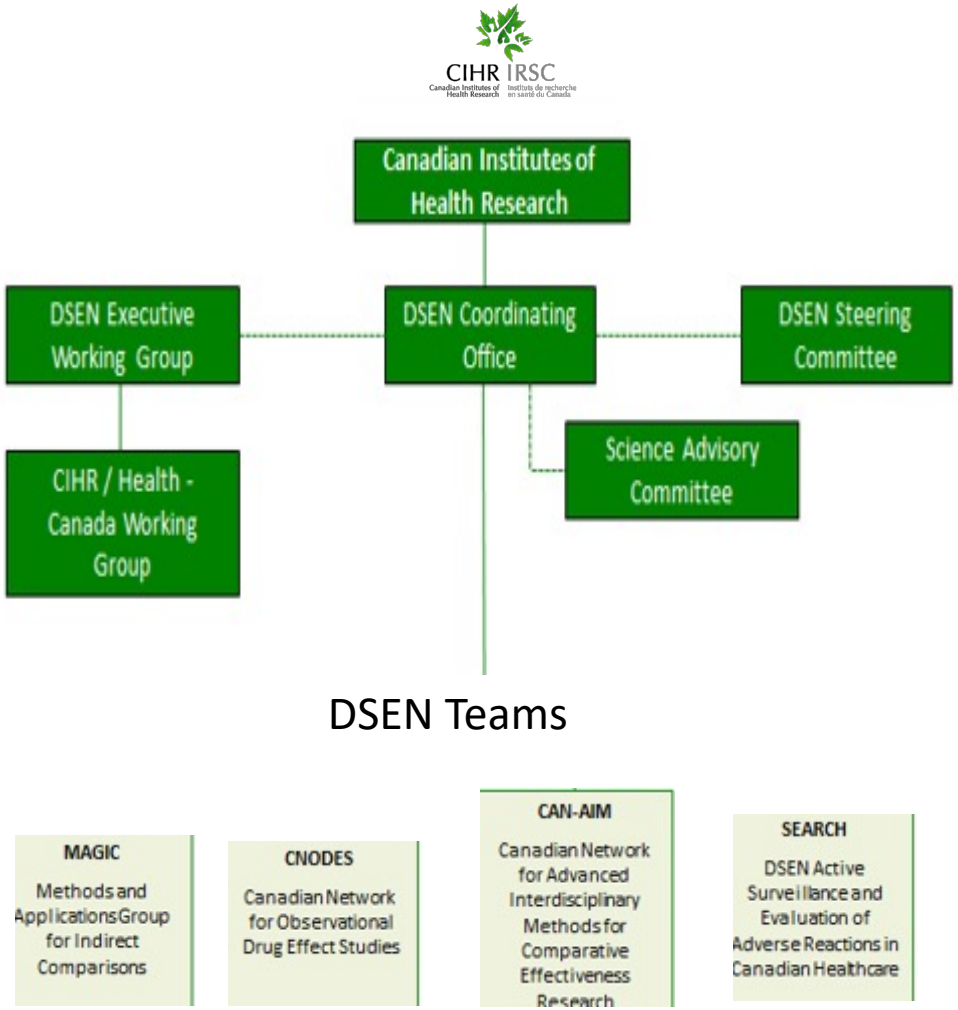
Drug Safety & Effectiveness Network (DSEN)

- Established by CIHR in collaboration with Health Canada and other stakeholders to:
  - Improve evidence on drug safety and effectiveness for regulators, policy-makers, providers, patients
  - Enhance capacity within Canada for high-quality post-market research on drug safety and effectiveness
- Up to the present, DSEN was hosted at CIHR; in 2022, the role of CIHR will be taken over by the Canadian Agency for Drugs & Technologies in Health, CADTH

Initiation of new DSEN projects ('queries')



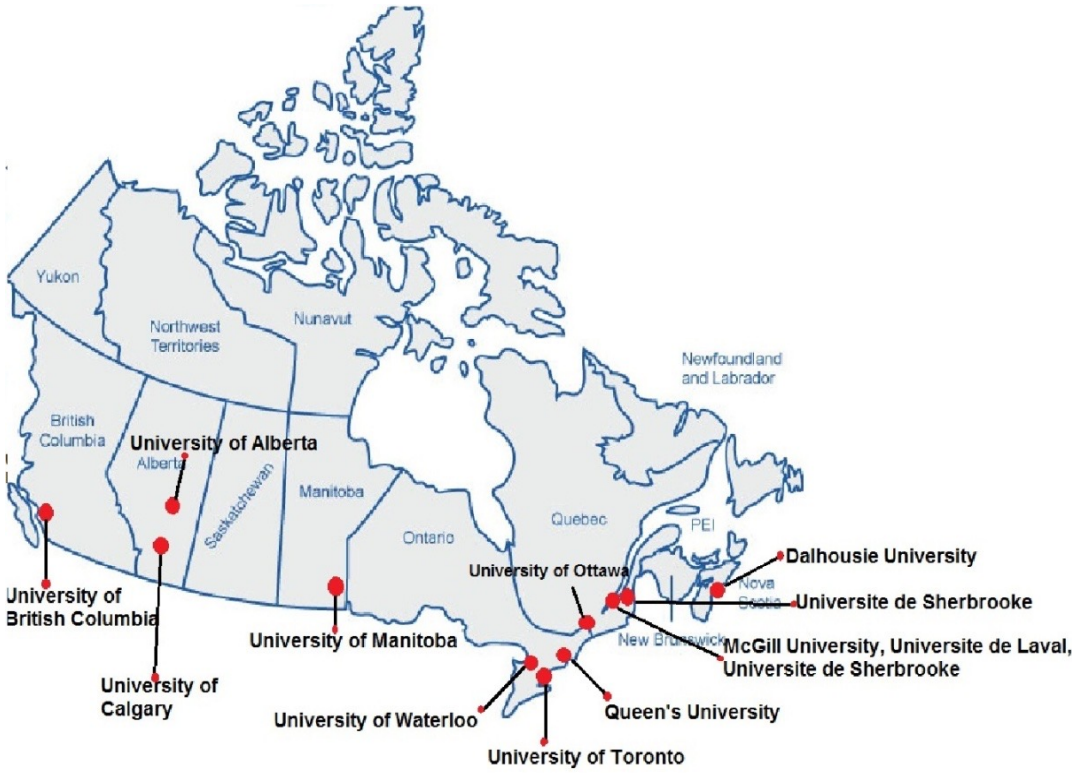


CAN-AIM Mission

Mission: Enhance Canadian research on real-world drug effectiveness and safety (cohorts)

- Challenges with observational data
  - Non-random allocation
  - Drug exposure definitions
  - 'Interval-censored data'
- Novel statistical **methods**, to avoid bias
- Vulnerable populations (e.g. pregnancy)
- **Build and enhance capacity** (trainees and highly qualified personnel)

Some CAN-AIM PIs
Michal Abrahamowicz PhD McGill
Louise Pilote MD MSc, McGill
Corinne Hohl MD MSc, UBC
Cristiano Moura Pharm PhD, McGill
Anick Berard, PhD, U de Montreal

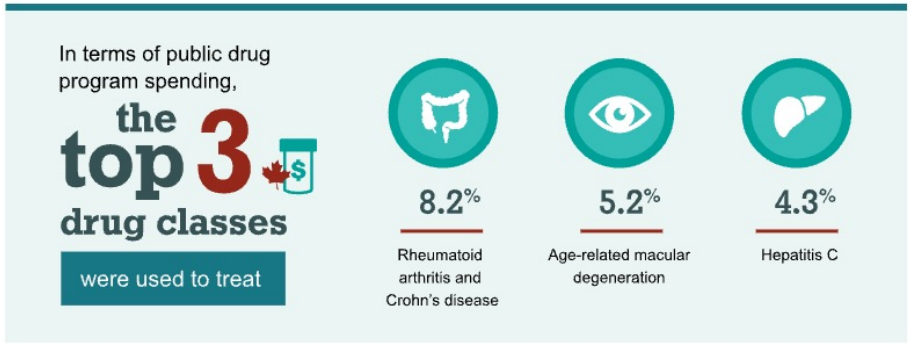


CAN-AIM Projects

- 2011-2014 Team Grant - Demonstration project: Drugs for Rheumatoid Arthritis
- 2015-2019 Team Grant - Renewal: Method development and capacity building
- 2020-2022 Team Grant - Renewal: Enhancing capacity building

To date, over 20 projects:

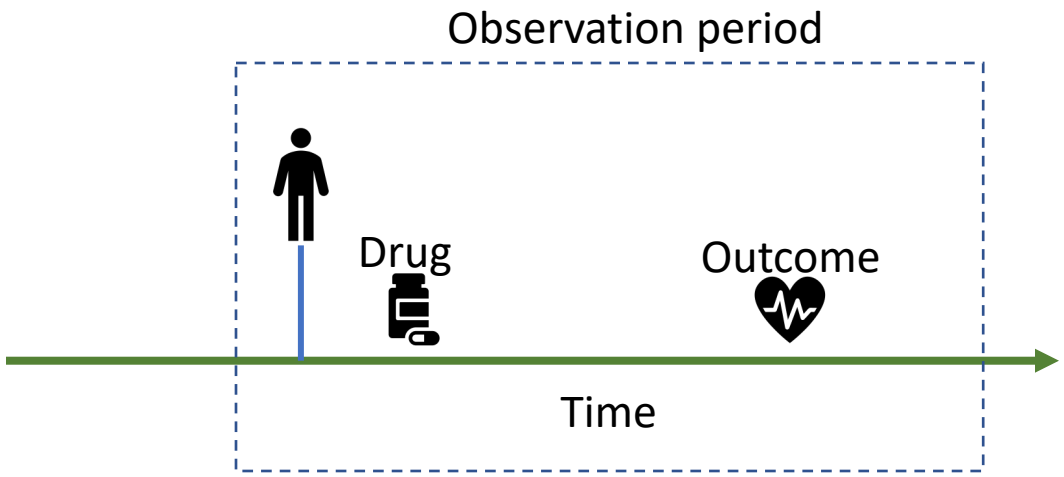
- Safety-adverse drug events
  - Vulnerable population (age, sex, comorbidity, SES)
  - Specific approaches for exposures during pregnancy
- Drug effectiveness: osteoporosis, DM, hypertension
- Special topics
  - Social media
  - Strategies to optimize prescription patterns
  - Opioid-related harms
- Biosimilars registry
- COVID-19 Projects:
  - *Reliability of COVID-19 case definitions in administrative and clinical databases*
  - *COVID-19 infection and medicines in pregnancy*
  - *Safety and immunogenicity of COVID-19 vaccines in pediatric autoimmune diseases*



Drug exposures in pharmacoepidemiology

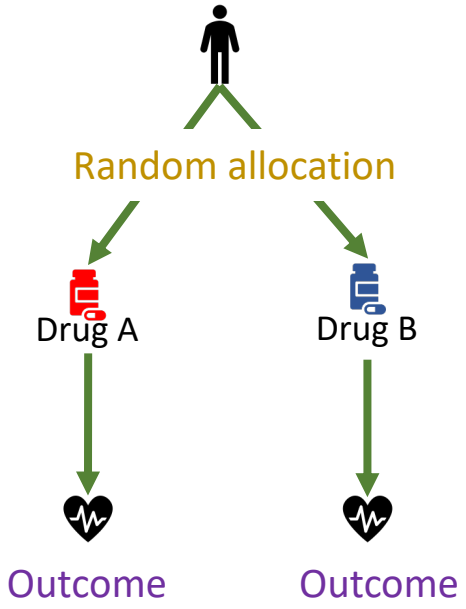
Drug exposures in pharmacoepidemiology

- Scope
  - Quantify the association between a drug exposure and a health outcome
  - Test causal relationship

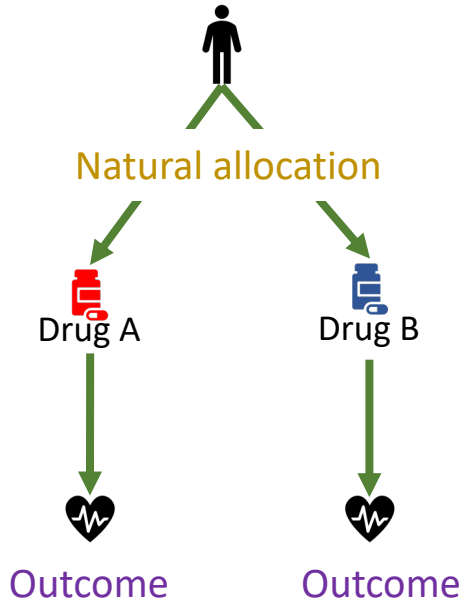


Drug exposures in pharmacoepidemiology

- Randomized Controlled Trial (RCT)



- Observational study (cohort)



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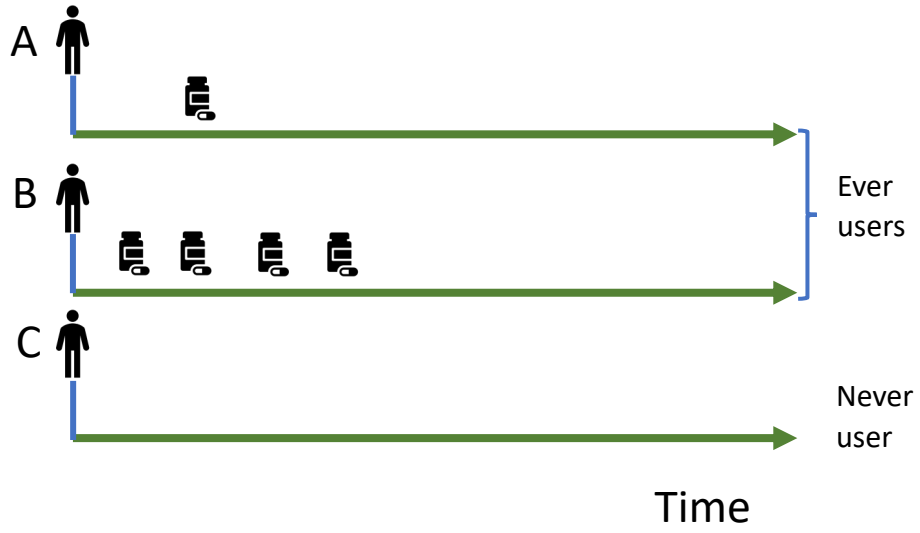
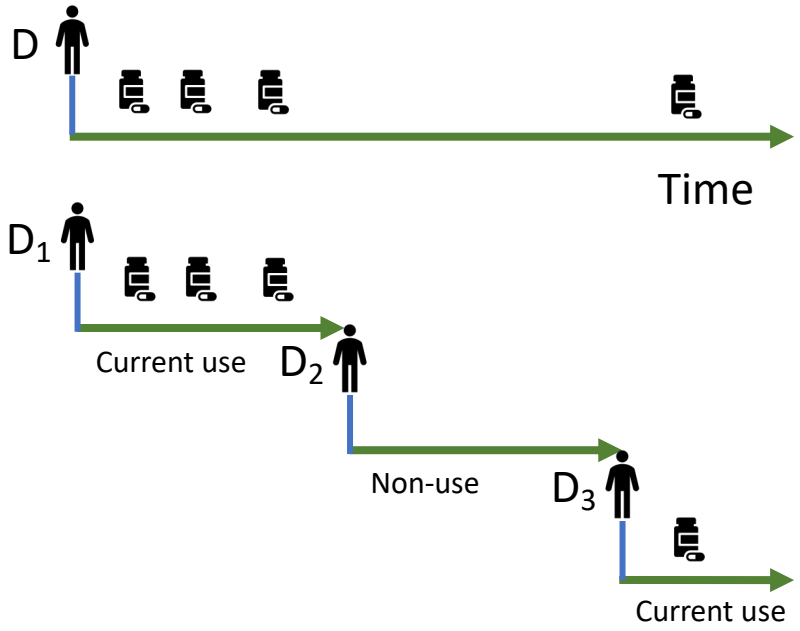
Drug exposures in pharmacoepidemiology

e.g. NSAIDs

- Time-fixed exposure
  - Ex.: Ever vs Never user



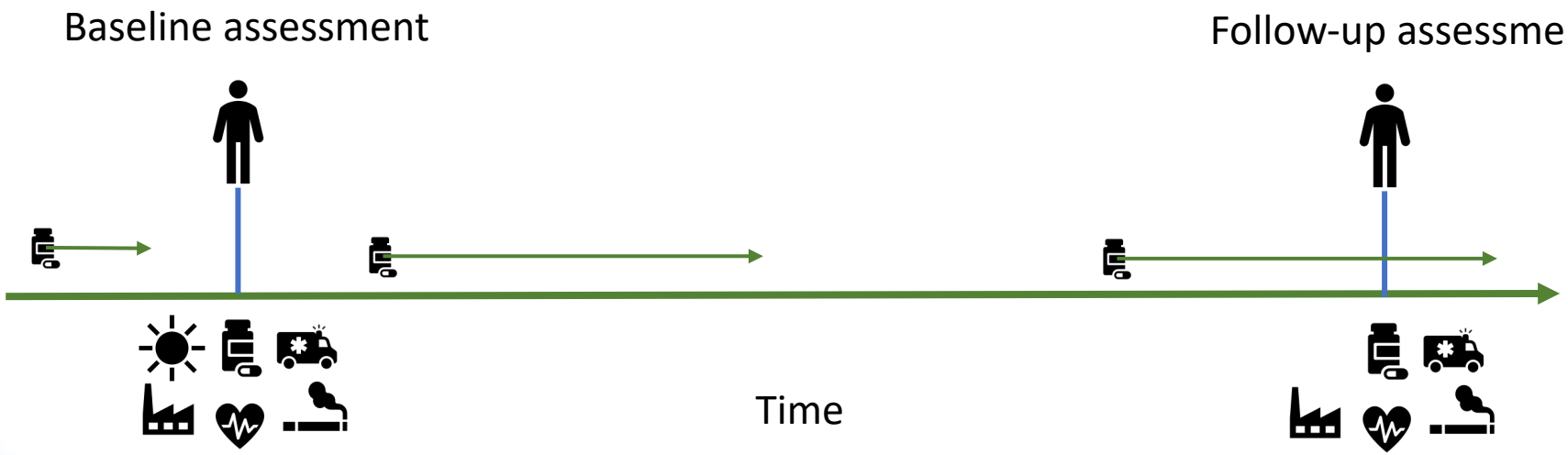
- Time-varying exposure
  - Current vs non-use



Data Linkage

Data Linkage: Key to optimizing CanPath data for drug safety and effectiveness research

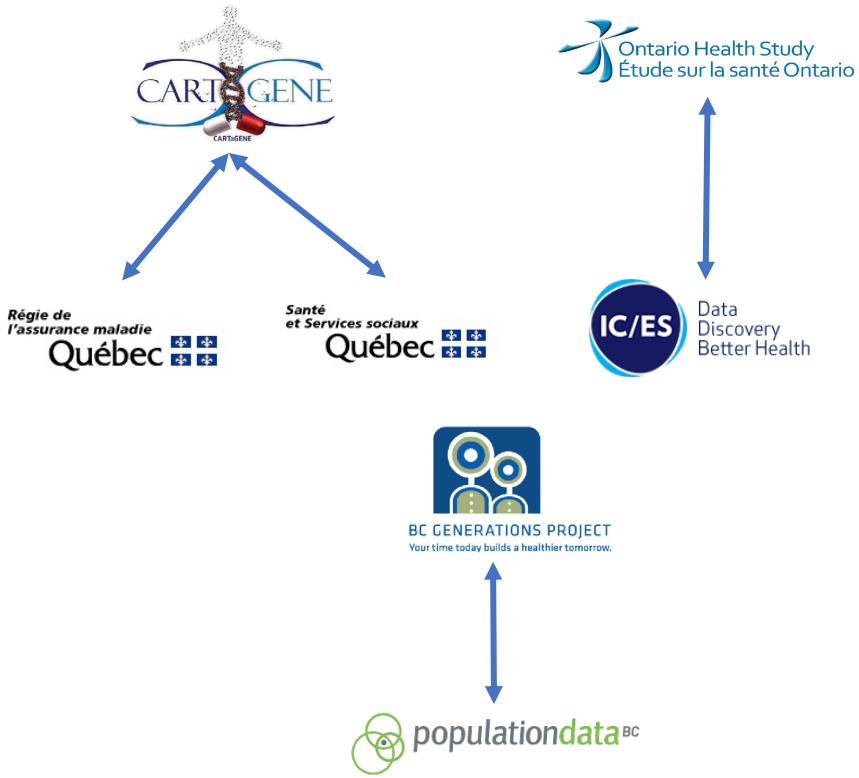
- Cohort study
  - Baseline and follow-up assessments via survey (key info on smoking, BMI, etc.)
  - Linkage with administrative health data (e.g. drugs dispensed, etc)



Data Linkage

- CanPath
  - Participants provided consent to follow-up through linkage with administrative health databases
    - Links to health care administrative data: additional information on participants' health from health care administrative databases (use of health services, such as physician visits or hospitalizations, drug use, and health outcomes, such as new diagnoses of cancer).

Data Linkage



CARTaGENE

- Data on 43,043 participants linked to Quebec provincial health administrative databases (1998 to 2021):
  - Regie de l'assurance maladie du Quebec (RAMQ)
    - Registered Persons Database
    - Drug Insurance Eligibility Period
    - **Pharmaceutical services (Services pharmaceutiques)**
    - Physician services
  - Ministère de la Santé et des Services sociaux (MSSS):
    - Hospital Stays, diagnostics, Services, ICU, Interventions
    - Death data

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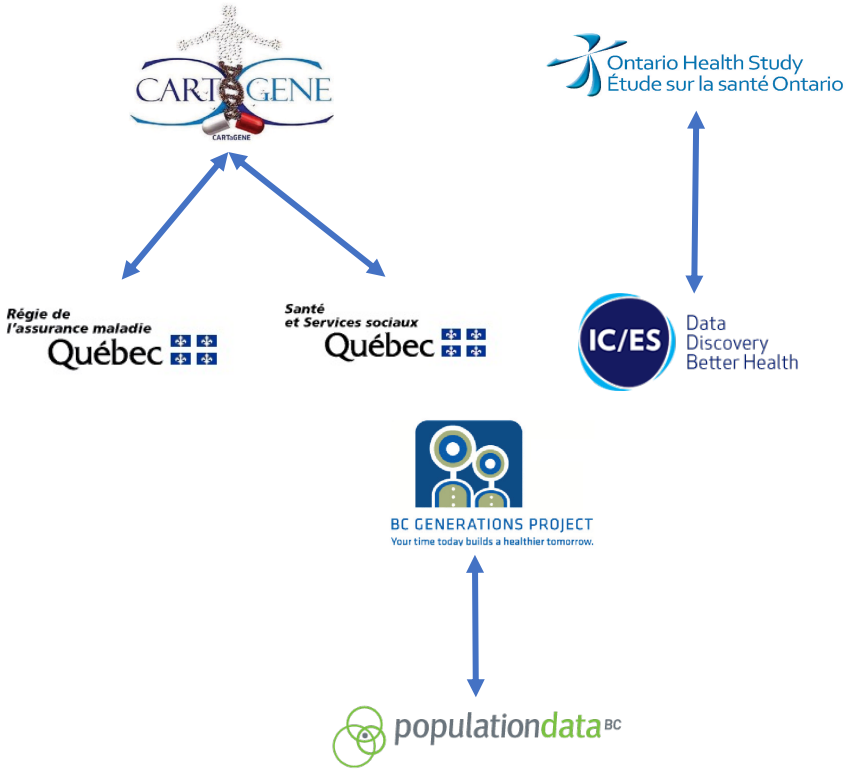
Data Linkage



Ontario Health Study (OHS)

- OHS data on 225,000 participants linked to IC/ES databases (from 2006 to 2016*):
  - Discharge Data Abstracts (DAD)
  - National Ambulatory Care Reporting System (NACRS)
  - Same Day Surgery (SDS)
  - Ontario Health Insurance Plan (OHIP)
  - Ontario Cancer Registry (OCR)
  - Registered Persons Database (RDP)
  - **Ontario Drug Benefit (ODB)**
  - **New Drug Funding Program (NDFP)**
  - Ontario Laboratory Information System (OLIS)

*2020 data expected Fall 2021

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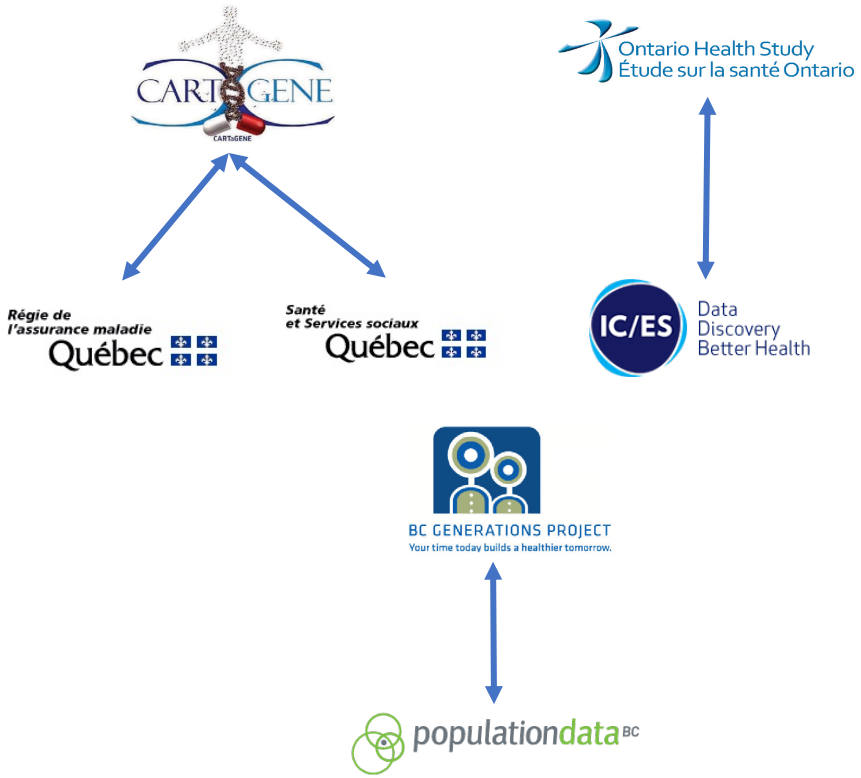
Data Linkage



BC Generations Project

- Data on ~30,000 participants was linked to Population Data BC (2020 data expected Fall 2021):
  - Population Data BC Medical Service Plan (Apr 1985 to Dec 2019)
  - Discharge Abstract Database (Apr 1985 to Dec 2019)
  - Consolidation File (Jan 1986 to Dec 2019)
  - Vital Statistics (Jan 2009 to Dec 2019)
  - **Pharmanet (Jan 1996 to Dec 2019)**

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Disclaimer: All inferences, opinions, and conclusions drawn in this presentation are those of the authors, and do not reflect the opinions or policies of the Data Stewards.

Different ways CanPath can be used for drug safety and effectiveness research

- A single point drug exposure (without using linkage with drug admin data) Cartagene -Hypertension analyses
- Agreement between self-reported information and claim database- Cartagene-Drugs
- Patterns of drug use – Illustration case with Ranitidine and other H2-blockers
- Longitudinal drug exposure and risk of outcomes – Non-melanoma skin cancer project

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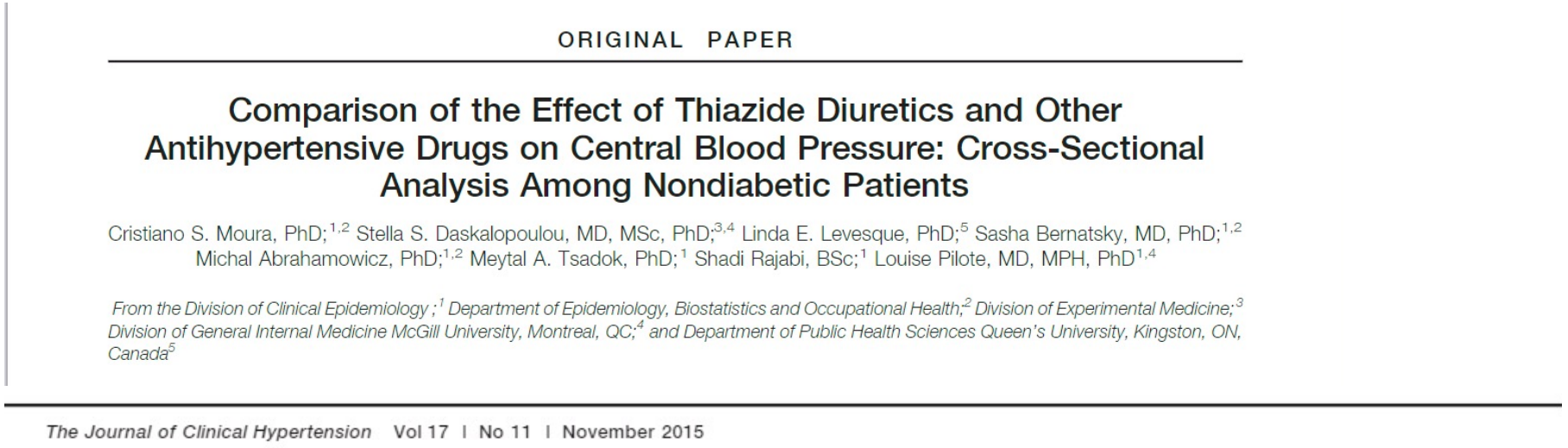
Cross-sectional analysis of antihypertensive use and blood pressure

- Objectives
  - Describe the association between current antihypertensive use and measurements of central blood pressure



ORIGINAL PAPER

Comparison of the Effect of Thiazide Diuretics and Other Antihypertensive Drugs on Central Blood Pressure: Cross-Sectional Analysis Among Nondiabetic Patients

Cristiano S. Moura, PhD;[1,2] Stella S. Daskalopoulou, MD, MSc, PhD;[3,4] Linda E. Levesque, PhD;[5] Sasha Bernatsky, MD, PhD;[1,2] Michal Abrahamowicz, PhD;[1,2] Meytal A. Tsadok, PhD;[1] Shadi Rajabi, BSc;[1] Louise Pilote, MD, MPH, PhD[1,4]

From the Division of Clinical Epidemiology ;[1] Department of Epidemiology, Biostatistics and Occupational Health;[2] Division of Experimental Medicine;[3] Division of General Internal Medicine McGill University, Montreal, QC;[4] and Department of Public Health Sciences Queen's University, Kingston, ON, Canada[5]

The Journal of Clinical Hypertension Vol 17 | No 11 | November 2015

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Cross-sectional analysis of antihypertensive use and blood pressure

- CARTaGENE 1st wave (20,000 participants)
  - Hypertensive, nondiabetic participants (self-reported)
  - Monotherapy use of one of four antihypertensive class of interest
    - Thiazide diuretics (TDs);
    - Calcium channel lockers (CCBs);
    - Angiotensin-converting enzyme inhibitors (ACEIs)
    - Angiotensin receptor blockers (ARBs)
- Blood pressure measurements
  - Peripheral and central measurements
  - Arterial stiffness (Augmentation Index [Aix])
- Multivariable linear models were used to compare means values of central blood pressure of TDs versus other antihypertensive monotherapies

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Cross-sectional analysis of antihypertensive use and blood pressure

- TD monotherapy was not associated with either statistically or clinically significantly higher levels of either pBP or cBP measurements when compared with monotherapy with other antihypertensive classes

- These findings highlighted the importance of diuretic agents as

one of the first- line therapies for uncomplicated hypertension

  - Inexpensive, effective drugs: Important knowledge for regulators, physicians, and patients

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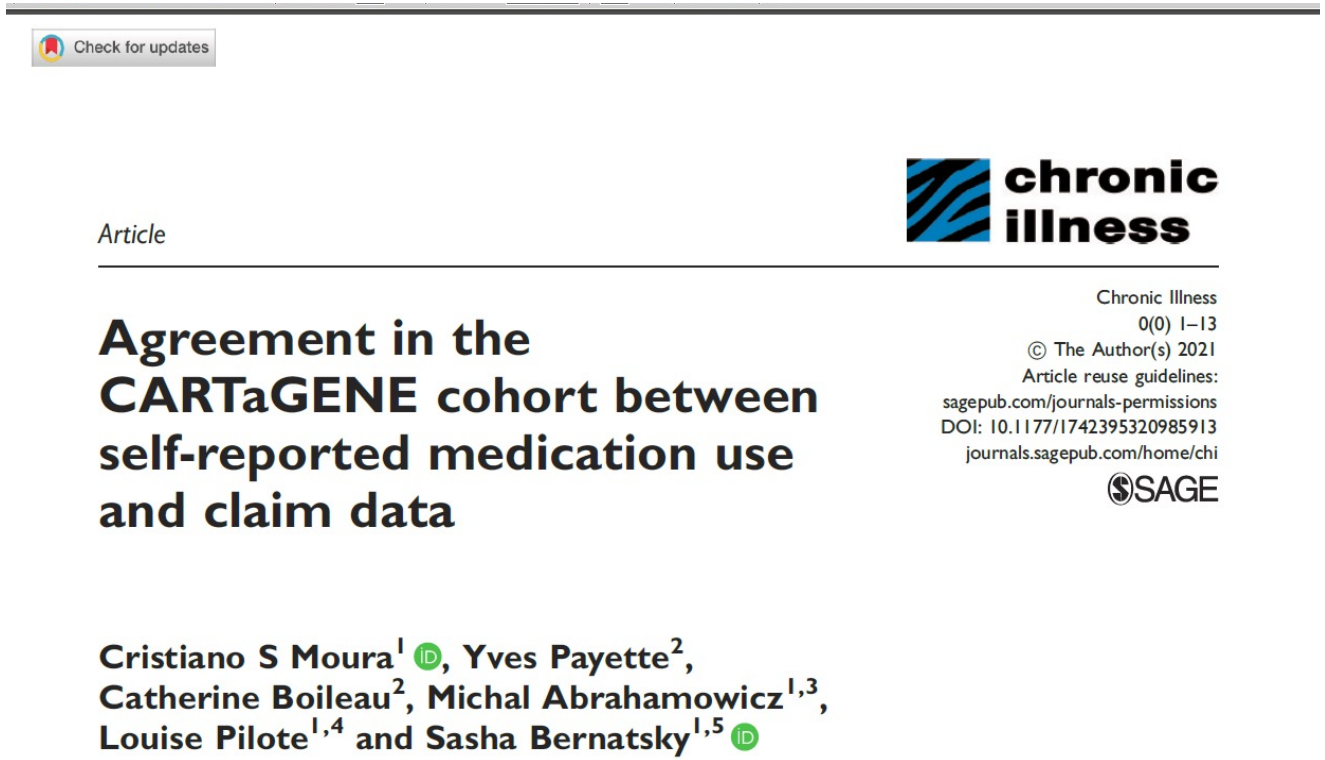
Agreement between self-reported medication and dispensation database

- Objectives
  - Describe the agreement of self-reported medication use with claim prescription records
    - Very important because at least 60% of patients don't take drugs as prescribed; and many also take drugs OTC
  - Determine factors associated with agreement between the two data sources.



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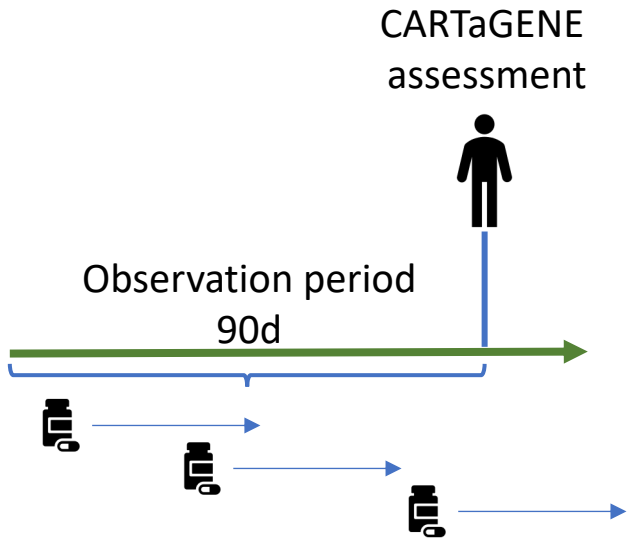
SAGE

Agreement in the CARTaGENE cohort between self-reported medication use and claim data

Cristiano S Moura[1], Yves Payette[2], Catherine Boileau[2], Michal Abrahamowicz[1,3], Louise Pilote[1,4] and Sasha Bernatsky[1,5]

Agreement between self-reported medication and dispensation database

- Self-reported medication data was obtained from CARTaGENE 1st wave (20,000 participants)
  - Original question: “Are you currently taking any prescribed medications?
- Data from CaG participants were linked to the RAMQ dispensation database.
  - This database contains data on outpatient prescribed medication, including name and dose, the date medication was dispensed.
- We compared all medications reported by CaG participants with prescription claims data extracted for the 90-day period previous to the CaG assessment date



Agreement between self-reported medication and dispensation database

- Agreement between self-reported medication use and administrative data varied considerably across medication classes (kappa 0.54 for respiratory system and 0.91 for systemic hormonal preparations).

- Female sex was associated with low agreement for some ATC groups

- High number of reported medications and heavy user of healthcare were associated with low agreement

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Prescription patterns of ranitidine in Canada

CanPath

Original query

- Background
  - Histamine H-2 receptor blockers, including ranitidine, are used to treat gastric reflux acid and ulcers (available over the counter and by prescription).
  - New safety concerns with ranitidine emerged in 2019, following the detection of N nitrosodimethylamine (NDMA), a potential human carcinogen, in some batches of that drug.
  - More evidence on the extent of exposure and utilization patterns could help estimate the risk of NDMA exposure attributable to the use of these drugs.

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Cohort selection

- *Objectives*
  - *What are prescription patterns of ranitidine, nizatidine, famotidine, and cimetidine in Canada?*
- *Cohort selection*
  - *Individuals from CanPath ever exposed to ranitidine, nizatidine, famotidine, and cimetidine (all histamine H2-receptor antagonists or H2 blockers) after cohort enrolment.*
  - *Individuals with drug coverage at the date of the 1st prescription.*

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Definition of period of use – Main analysis

- Follow-up started at the first dispensation of one drug of interest
  - Dispensation records issued during the follow-up time were used to create periods of use, defined as continuous use with no interruption and no change in dose.
    - Individuals could contribute with multiple periods of use until the end of follow-up (end of coverage in the drug plan, death, or cohort end date).
    - Overlapping periods between dispensations (due to early refill) were considered for the calculation of the end period.
    - In case a new period of use was initiated because of a change in the dose, any remaining “days” were added at the end of the previous period of use.
    - The end of period occurred either when there was a gap of one or more days between dispensations (after the correction for early refill) or a change in dose.

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Analyses

- Baseline description of studied individuals.
- Patterns of use during follow-up and 1st year of use
  - Observed period since first prescription;
  - Number of periods of uninterrupted use;
  - Cumulative duration of use, in days;
  - The average duration of periods of use, in days;
  - Cumulative dose, total amount of drug dispensed, in mg;
  - The Prescribed Daily Dose (PDD);
  - The Defined Daily Dose (DDD).
    - “The assumed average maintenance dose per day for a drug used for its main indication in adults.” (WHO)

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Sensitivity analyses

- Doses (in DDD)
  - A change in dose would immediately result in the end of the period of use (i.e., disregarding any remaining stockpiling of the old prescription);
  - A new period of use starting because of change in dose was only initiated if the difference between current and new dose > |0.3|;
- Gaps allowed between prescriptions;
  - 14, 30, or **90 days**

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Results – baseline characteristics

- In OHS, 3538 users of H2 blockers (7.1% of eligible participants)
  - 93.8% were ranitidine users (considering the 1st drug being dispensed
  - 53.9% women, and 63% were 65 years or older (at cohort enrollment date)
- In CaG, there were 1,042 users (6.4% of eligible participants)
  - 94.0% were ranitidine users
  - 63.4% women, , with mean age of 58.5 years (SD=7.6)
- In BCGP, there were 2,340 users (7.8% of eligible participants)
  - 96.4% were ranitidine users
  - 74.1% were women, with mean age of 57.4 years (SD=8.7)

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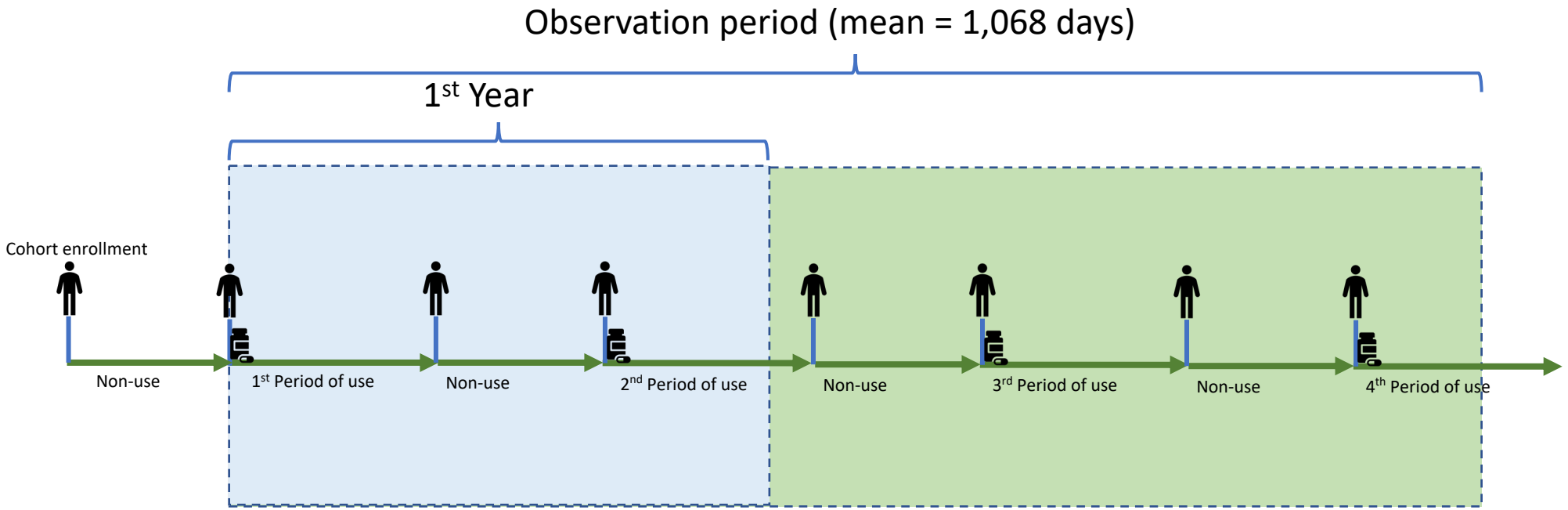
Results – patterns of use

- All H2 blockers - OHS



In the 1st Year

- *There were 1.9 periods of use*
- *Total duration of use was 141 days, with 133 DDDs*
- *Each period of use lasted for 76 days, with 71 DDDs*

During the entire follow-up

- *There were 3.4 periods of use*
- *Total duration of use was 384 days, with 361 DDDs*
- *Each period of use lasted for 110 days, with 104 DDDs*

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Conclusions

- Describing patterns of drug use for regulators is feasible using CanPath data: Illustrates a great use of linked drug data
- In all three cohorts, ranitidine was the H2 blocker most largely used by participants with drug coverage in provincial drug plans
- Participants were intermittent users of these drugs
  - Intercalated periods of use and non-use
- Doses were mostly within recommended dose
- Information has been reported back to Health Canada for their use

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Potential limitations

- With linked data, we are able to study only those with provincial drug benefits (e.g. in ON-seniors) not data from private sectors
- Current analysis restricted to prescribed medication and does not include over-the-counter drugs.
- Self-reported CanPath medication data could potentially help address these points?

Summary

- All are affected by drug safety and effectiveness at some point
- CanPath data can be used to help regulators regarding optimizing medication-related outcomes in Canada…
- However, many challenges when using CanPath and other secondary data sources, to study drug safety and effectiveness
- This highlights the importance of DSEN teams like CANAIM, to thoughtfully consider potential limitations of data and use best practices in attempts to overcome these
- Building and enhancing capacity (trainees and highly qualified personnel) is key to ensuring that Canada continues to be a leader in drug safety and effectiveness research

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Thank you – Merci – Obrigado