Introducing CoLab: The Evolution of US-Canada International Collaboration on Drug Safety and Effectiveness

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Judith Maro, PhD – Assistant Professor, Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School

Tarry Ahuja, PhD – Director, Post-Market Drug Evaluation, Canadian Agency for Drugs and Technologies in Health

Kristian Filion, PhD – Associate Professor, McGill University

Disclosures

David Moeny, MPH

This presentation reflects the views of the author and should not be construed to represent U.S. FDA's views or policies.

Melissa Kampman, PhD

This presentation reflects the views of the author and should not be construed to represent Health Canada's views or policies.

Judith Maro, PhD

Nothing to disclose.

Tarry Ahuja, PhD

This presentation reflects the views of the author and should not be construed to represent CADTH's views or policies.

Kristian Filion, PhD

Nothing to disclose.

Introducing CoLab: The Evolution of US-Canada International Collaboration on Drug Safety and Effectiveness

Food and Drug Administration Perspective

David Moeny, MPH, R.Ph
Deputy Director,
Office of Pharmacovigilance and Epidemiology
August 25, 2023

Overview

- Quick Sentinel data overview
- Example collaboration:
  utilization study of valsartan nitrosamine impurities

This disclaimer will be provided in a joint disclaimer slide in the first presentation of the symposium

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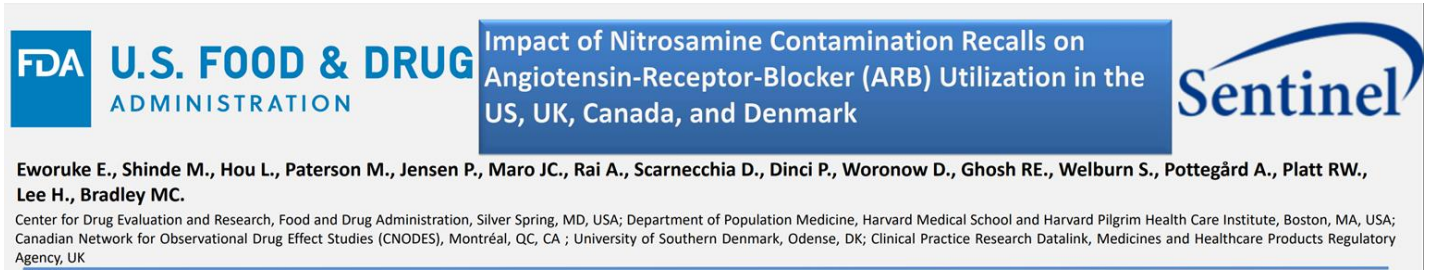
US – Canada Examples of Collaboration



FDA U.S. FOOD & DRUG ADMINISTRATION

Impact of Nitrosamine Contamination Recalls on Angiotensin-Receptor-Blocker (ARB) Utilization in the US, UK, Canada, and Denmark

Sentinel

Eworuke E., Shinde M., Hou L., Paterson M., Jensen P., Maro JC., Rai A., Scarnecchia D., Dinci P., Woronow D., Ghosh RE., Welburn S., Pottegård A., Platt RW., Lee H., Bradley MC.

Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA; Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA ; University of Southern Denmark, Odense, DK; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Agency, UK

Reproducing Protocol-Based Studies Using Parameterizable Tools—Comparison of Analytic Approaches Used by Two Medical Product Surveillance Networks

Ting-Ying Huang[1,*], Emily C. Welch[1], Mayura U. Shinde[1], Robert W. Platt[2], Kristian B. Filion[2,3,4], Laurent Azoulay[2,3,5], Judith C. Maro[1], Richard Platt[1] and Sengwee Toh[1]

The US Sentinel System and the Canadian Network for Observational Drug Effect Studies (CNODES) are two medical product safety surveillance networks. Using Sentinel's preprogrammed, parameterizable analytic tools, we reproduced two protocol-based studies conducted by CNODES to assess the risks of acute pancreatitis and heart failure (HF) associated with the use of incretin-based drugs, compared with use of ≥ 2 oral hypoglycemic agents. Results from the replication new-user cohort analyses aligned with those from the CNODES nested case-control studies. The adjusted hazard ratios were 0.95 (0.81–1.12; vs. 1.03 (0.87–1.22) in CNODES) for acute pancreatitis and 0.91 (0.84–1.00; vs. 0.82 (0.67–1.00) in CNODES) for HF among patients without HF history. The CNODES's common protocol approach allows studies tailored to specific safety questions, whereas the Sentinel's common data model plus pretested program approach enables more rapid analysis. Despite these differences, it is possible to obtain comparable results using both approaches.

Open access Original research

BMJ Open

Valsartan, Losartan and Irbesartan use in the USA, UK, Canada and Denmark after the nitrosamine recalls: a descriptive cohort study

Efe Eworuke ,[1] Mayura Shinde,[2] Laura Hou,[2] Michael J Paterson,[3] Peter Bjødstrup Jensen,[4] Judith C Maro,[2] Ashish Rai,[2] Daniel Scarnecchia ,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca E Ghosh,[5] Stephen Welburn ,[5] Anton Pottegard,[6,7] Robert W Platt,[2] Hana Lee,[1] Marie C Bradley [1]

https://www.sentinelinitiative.org/news-events/publications-presentations/impact-nitrosamine-contamination-recalls-angiotensin

Clin Pharmacol Ther. 2020 Apr;107(4):966-977. doi: 10.1002/cpt.1698. Epub 2019 Dec 12.

BMJ Open. 2023 Apr 17;13(4):e070985. doi: 10.1136/bmjopen-2022-070985.

Sentinel Data Philosophy

Sentinel Common Data Model (SCDM) is designed to meet regulatory needs for analytic flexibility, transparency, and control

Flexible: Adapts to ever-changing priorities

- Predominantly claim-based, but allows electronic health record (EHR), registry, survey, and free-text data

Transparent: Distinct data types kept separate with minimal mapping

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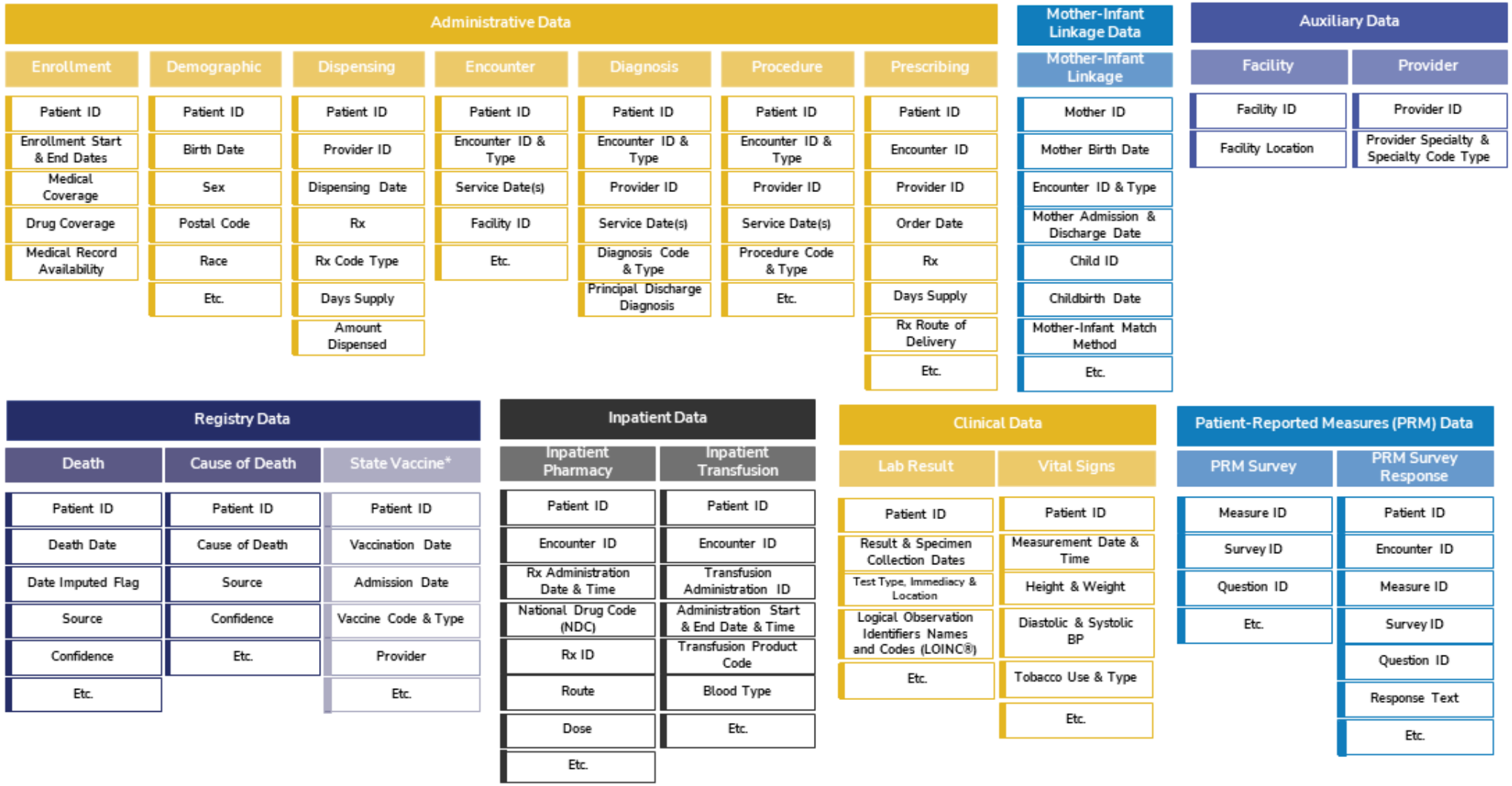
Control: Data Partners work closely with Sentinel Operations Center when populating tables

- Appropriate use and interpretation of local data requires the Data Partners' local knowledge and data expertise

Sentinel Common Data Model



*The State Vaccine table has not been in use since SCDM v6.0.

https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Following a Patient in the Sentinel Common Data Model

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	ZIP
PatID1	02/02/1984	F	N	5	32818
PatID2	05/02/2006	M	N	5	32818

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2018	Y	Y
PatID2	6/1/2006	12/31/2018	Y	Y

DISPENSING

PATID	RXDATE	NDC	RXSUP	RXAMT
PatID1	10/14/2005	00006074031	30	30
PatID1	10/14/2005	00185094098	30	30
PatID1	10/17/2005	00378015210	30	45
PatID1	10/17/2005	54092039101	30	30
PatID2	03/02/2016	54868056400	10	10

ENCOUNTER

PATID	ENCOUNTERID	ADATE	DDATE	ENCTYPE
PatID1	EncID1	10/18/2005	10/20/2005	IP
PatID1	EncID2	05/02/2006	05/03/2006	IP
PatID2	EncID1	03/02/2016	.	AV

DIAGNOSIS

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	DX	DX_CODETYPE	PDX
PatID1	EncID1	10/18/2005	Provider1	IP	296.2	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	300.02	9	S
PatID1	EncID2	5/2/2006	Provider1	IP	V30.00	9	P
PatID2	EncID1	03/02/2016	Provider2	AV	H66.13	10	X

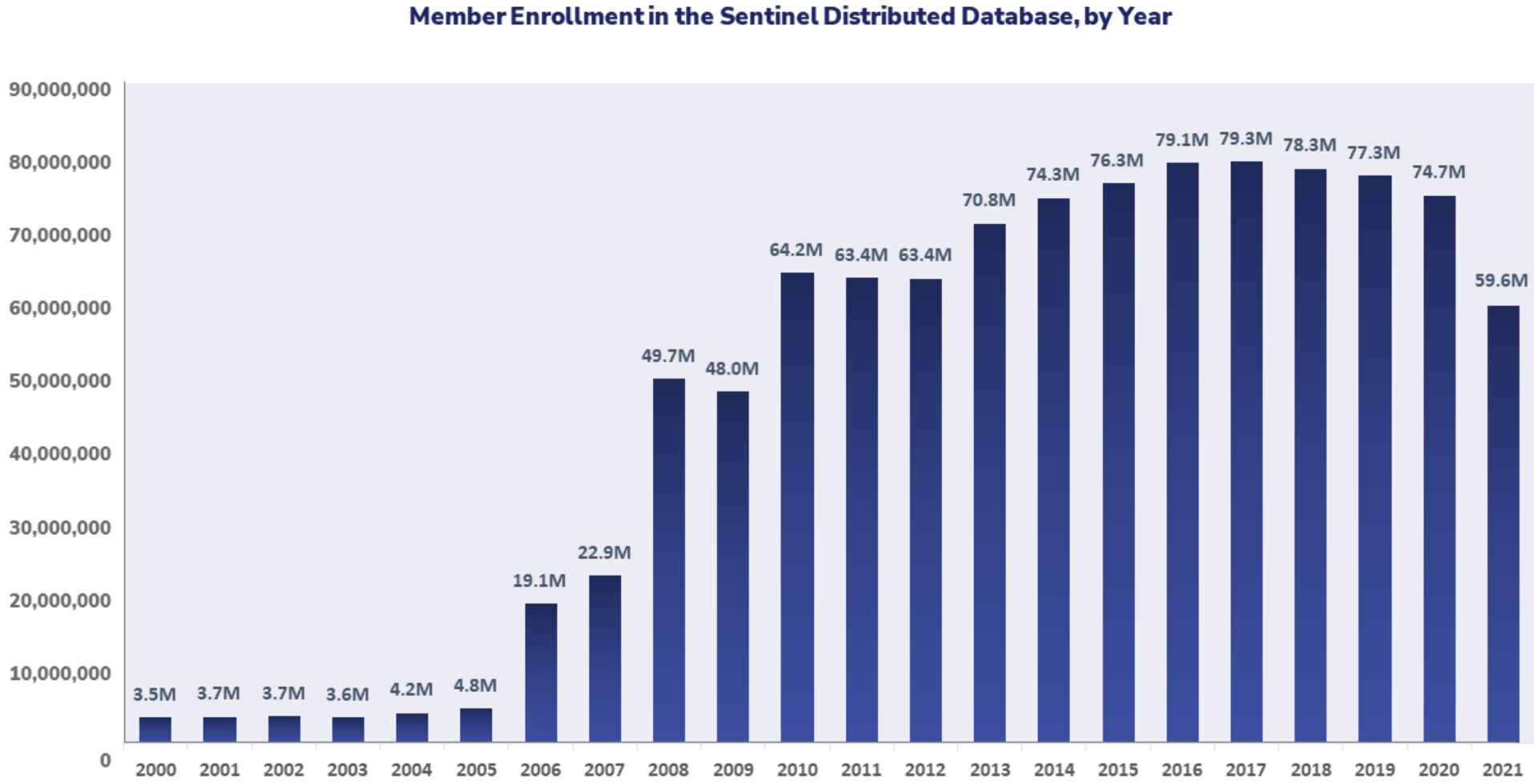
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4
PatID1	EncID2	05/02/2006	Provider1	IP	59400	C4
PatID2	EncID1	03/02/2016	Provider2	AV	99203	C4

MOTHER-INFANT LINKAGE

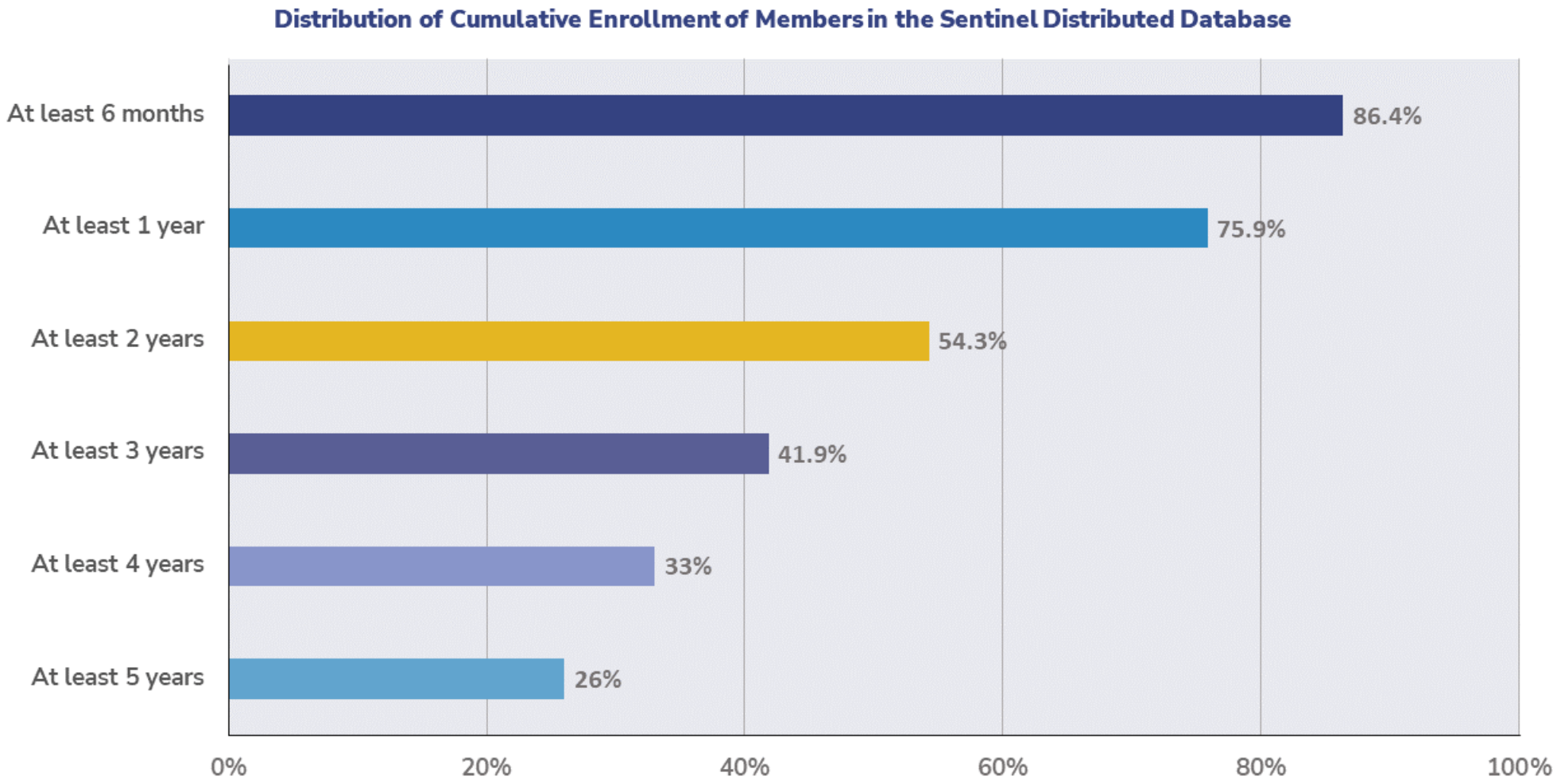
MPATID	ADATE	DDATE	CPATID	CBIRTH_DATE	CSEX	CENR_START	BIRTH_TYPE	MATCHMETHOD
PatID1	5/2/2006	5/3/2006	PatID2	5/2/2006	M	6/1/2006	1	SI

Bigger is Better!



https://www.sentinelinitiative.org/about/key-database-statistics#member-enrollment-in-the-sentinel-distributed-database-by-year

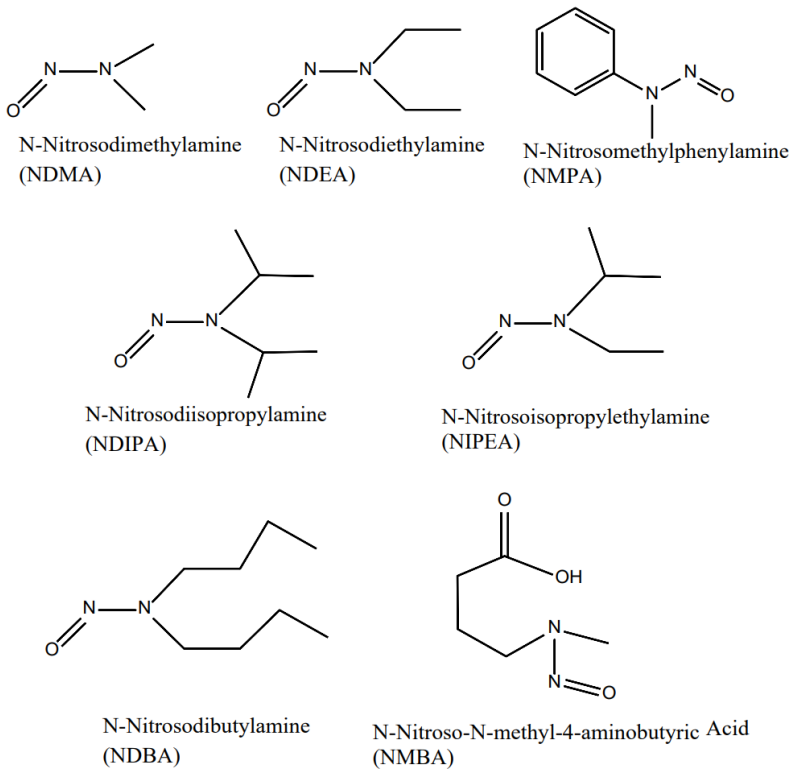
Is it Always?



https://www.sentinelinitiative.org/about/key-database-statistics#distribution-of-cumulative-enrollment-of-members-in-the-sentinel-distributed-database

Nitrosamine Impurities in Valsartan

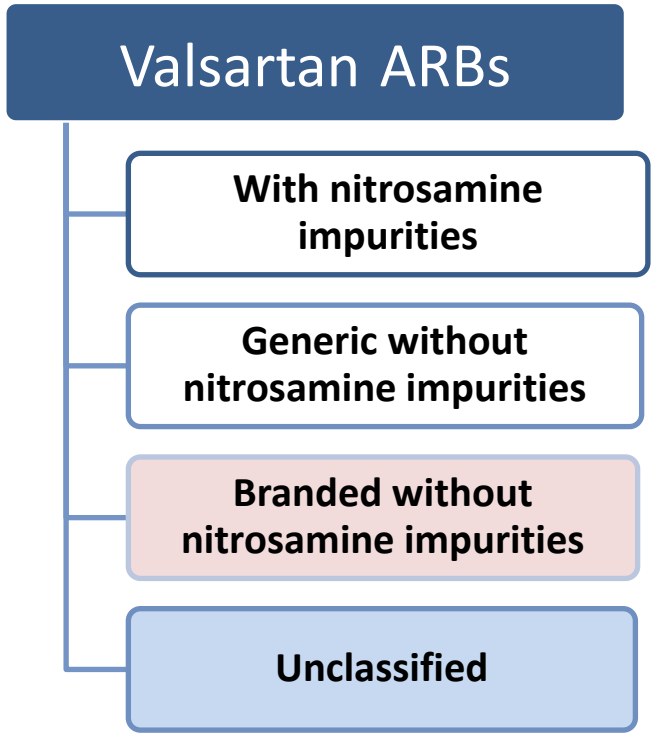
Figure 2. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products



- In July 2018, the U.S. FDA and other international regulatory agencies issued a recall of valsartan, an angiotensin receptor blocker (ARBs) containing N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) impurities
- Subsequently, other ARBs including irbesartan and losartan were recalled in October and November 2018 in US and Jan-March 2019 in Canada
- Regulatory agencies emphasized in their communications that patients should not abruptly stop their medication.
- Despite timely dissemination of recall notices, little is known about the impact of recall and how patients and prescribers responded to the notices.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

Exposure Definition



Nitrosamine impurities product classifications

Sentinel US

Generic valsartan without nitrosamine impurities

- NDC codes corresponding to each product that had NDMA/NDEA impurity detected

Non-Recalled Generic valsartan

- NDCs for products that had no NDMA/NDEA detected

Non-Recalled Branded valsartan

- Included valsartan products from Novartis and Sandoz manufacturers with no NDMA/NDEA detected

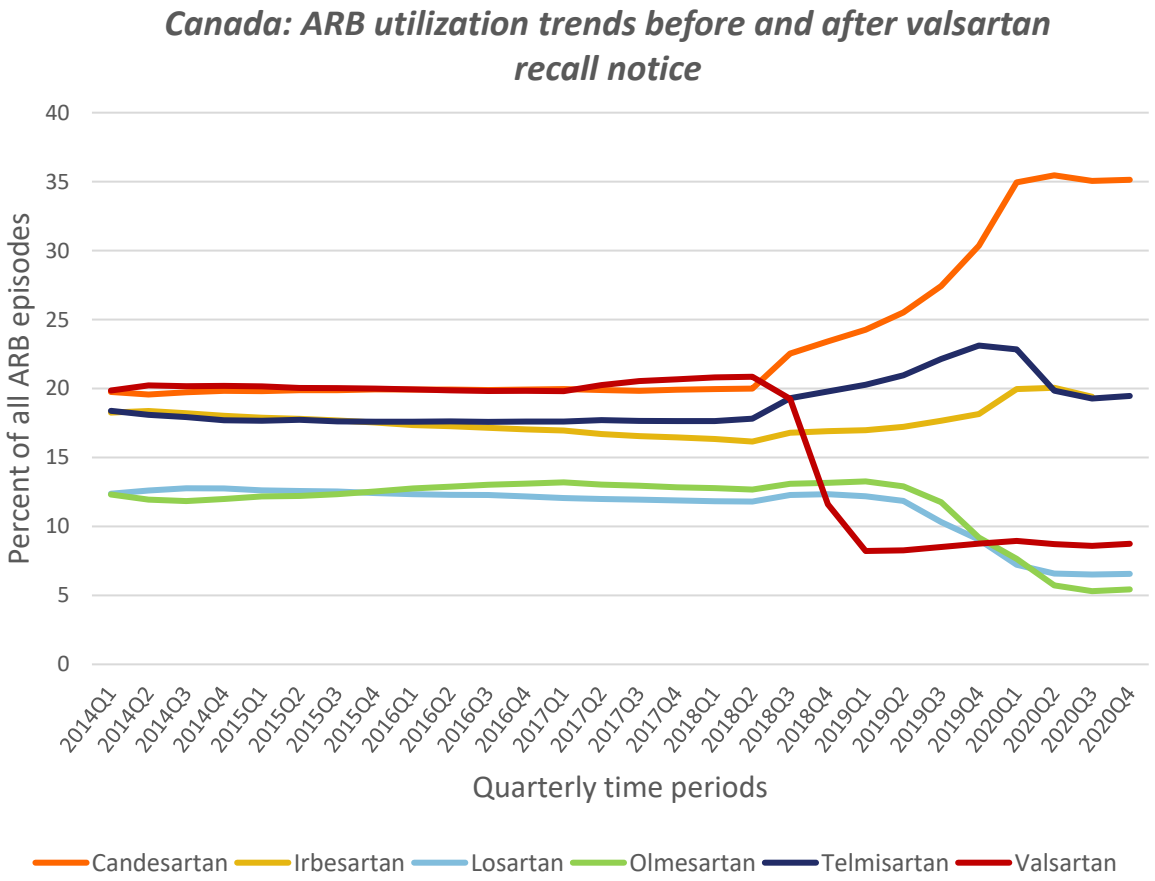
Recalled valsartan / Recalled ARBs

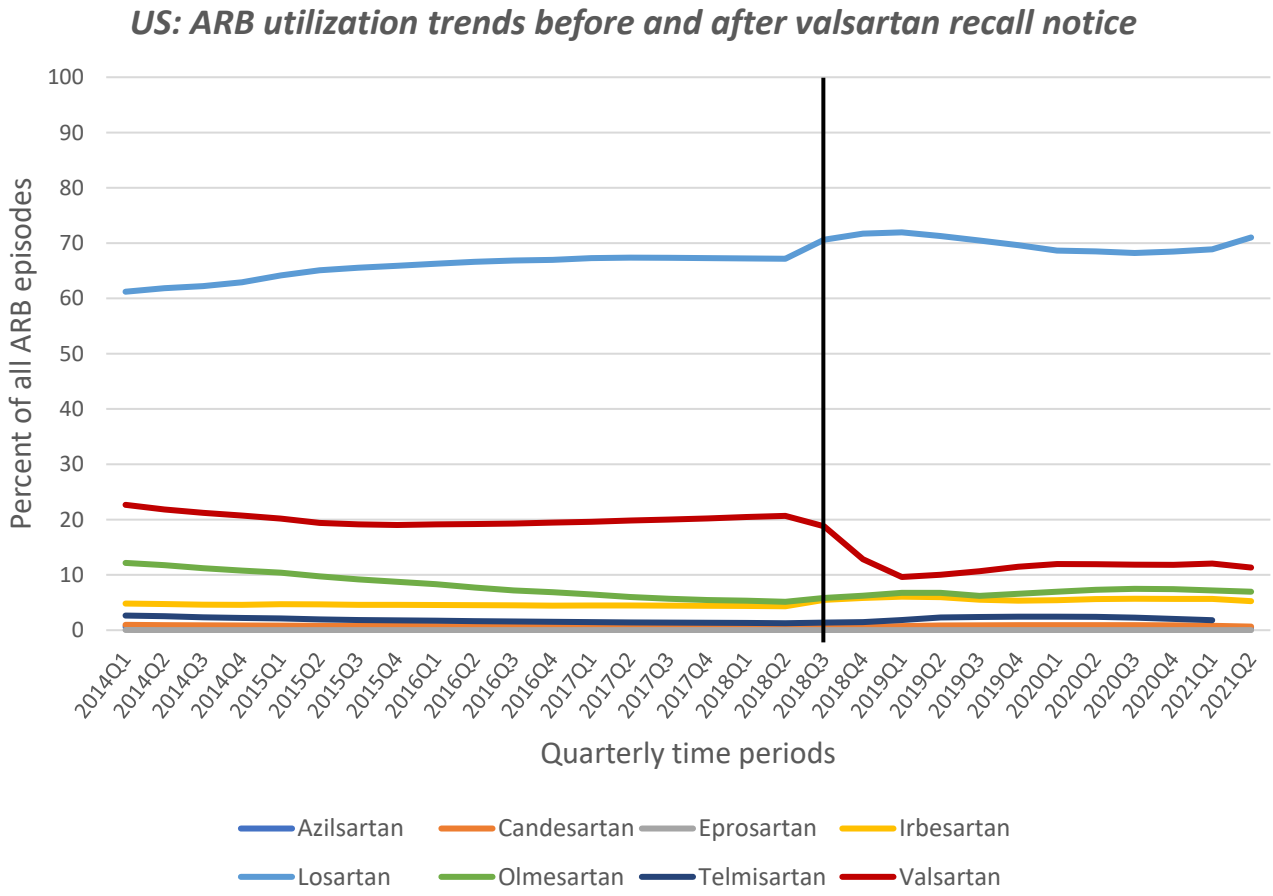
Unclassified Valsartan included any remaining valsartan products

CNODES (Canada)

DIN codes for valsartan products with impurities, without impurities or recalled

Angiotensin Receptor Blocker Utilization Over Time

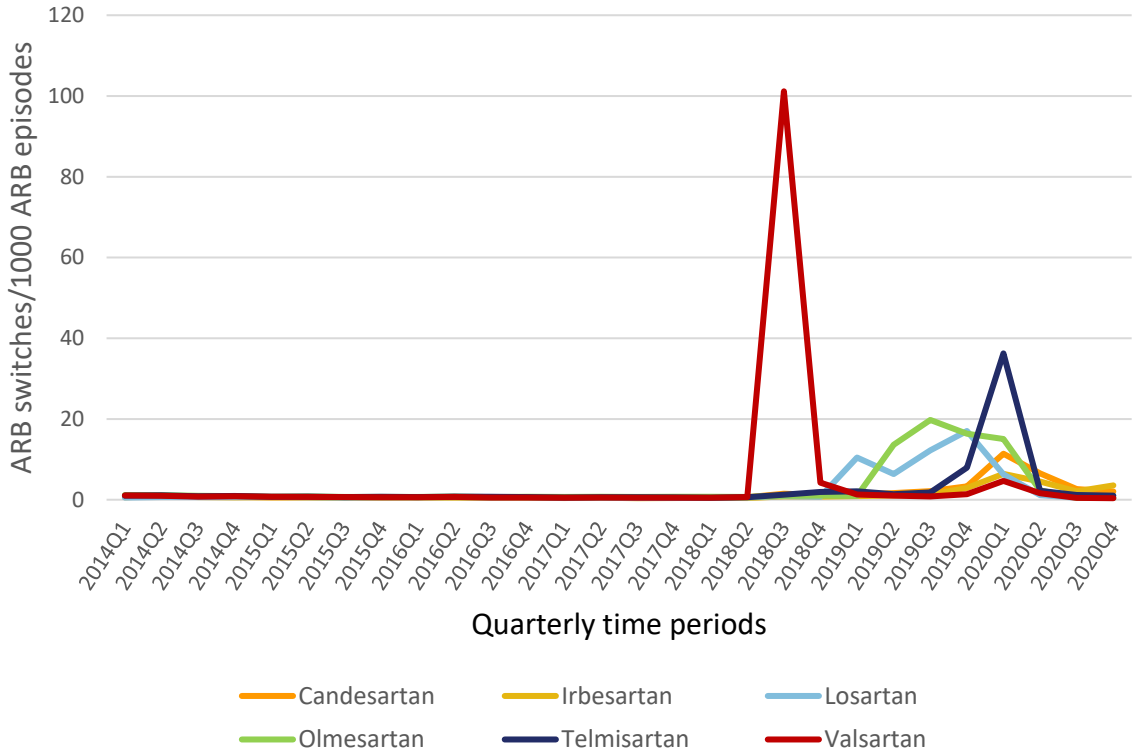




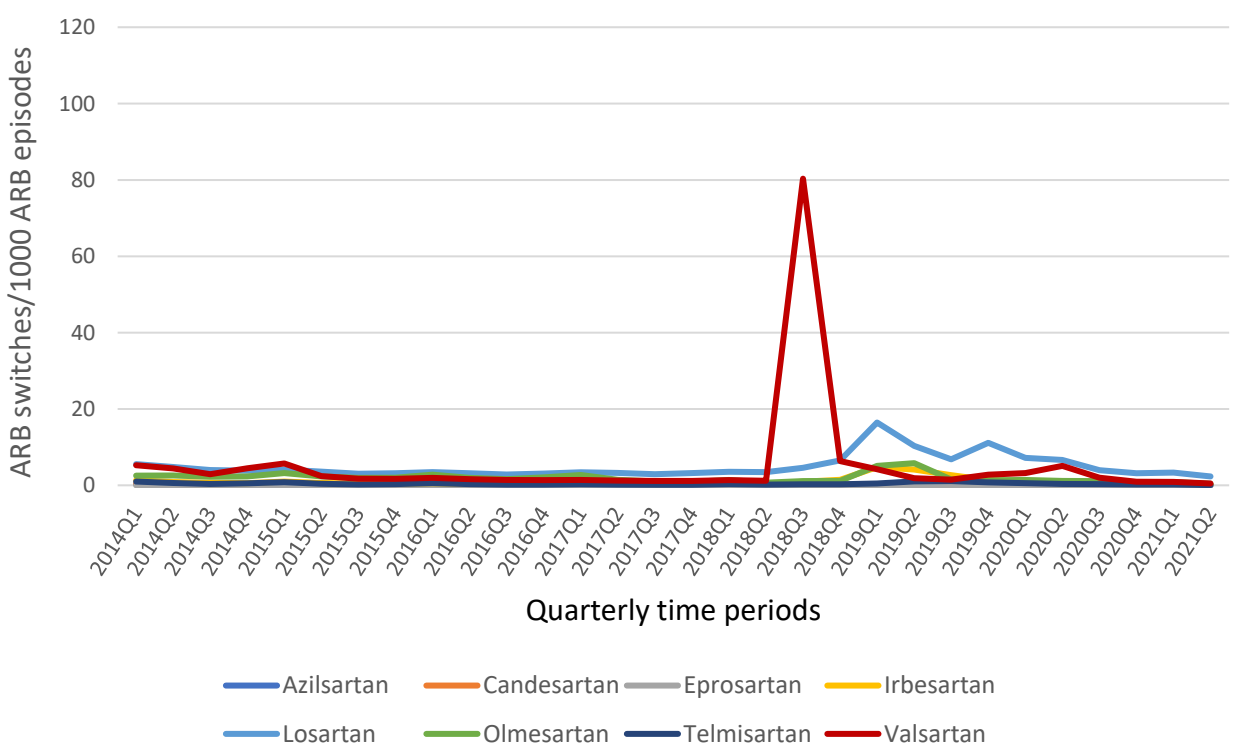
BMJ Open. 2023 Apr 17;13(4):e070985. doi: 10.1136/bmjopen-2022-070985.

Switching from Valsartan

Canada trends: Quarterly proportion of switching from one ARB to another ARB



US trends: Quarterly proportion of switching from one ARB to another ARB

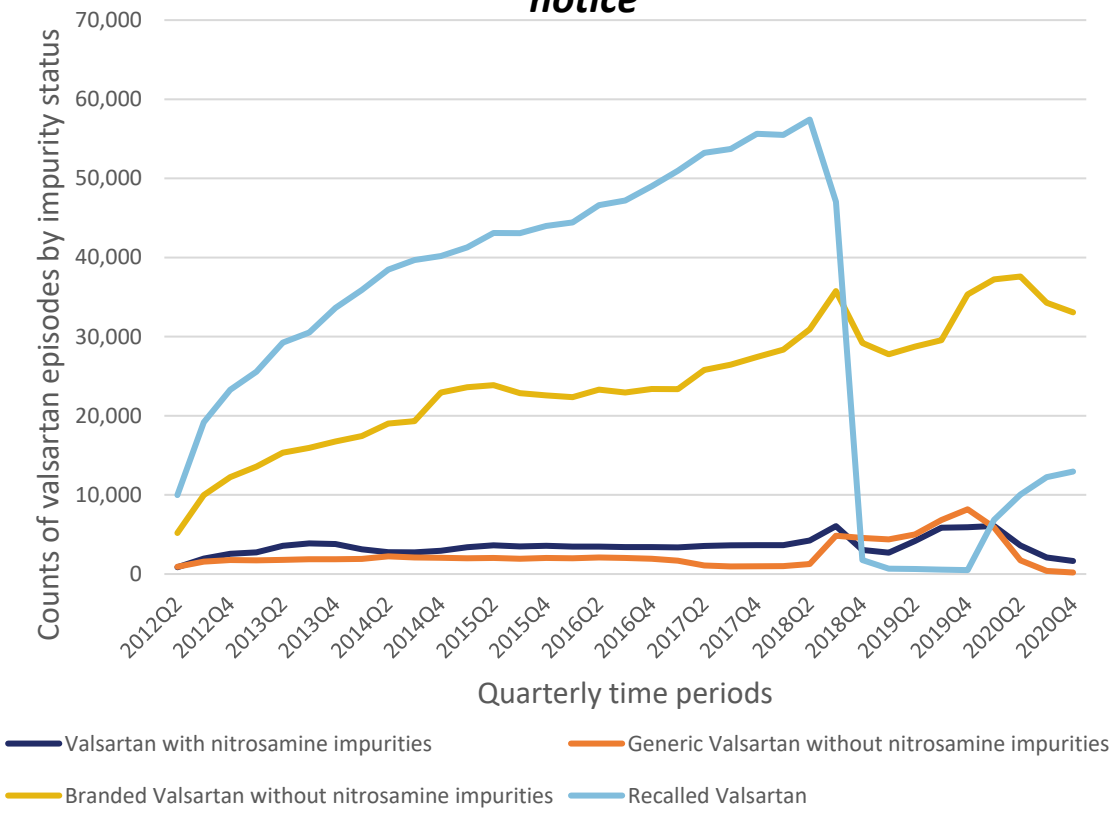


- Increased switching of valsartan to other ARBs noted in 2018 Q3, following recall notice in July 2018 in the U.S. and Canada

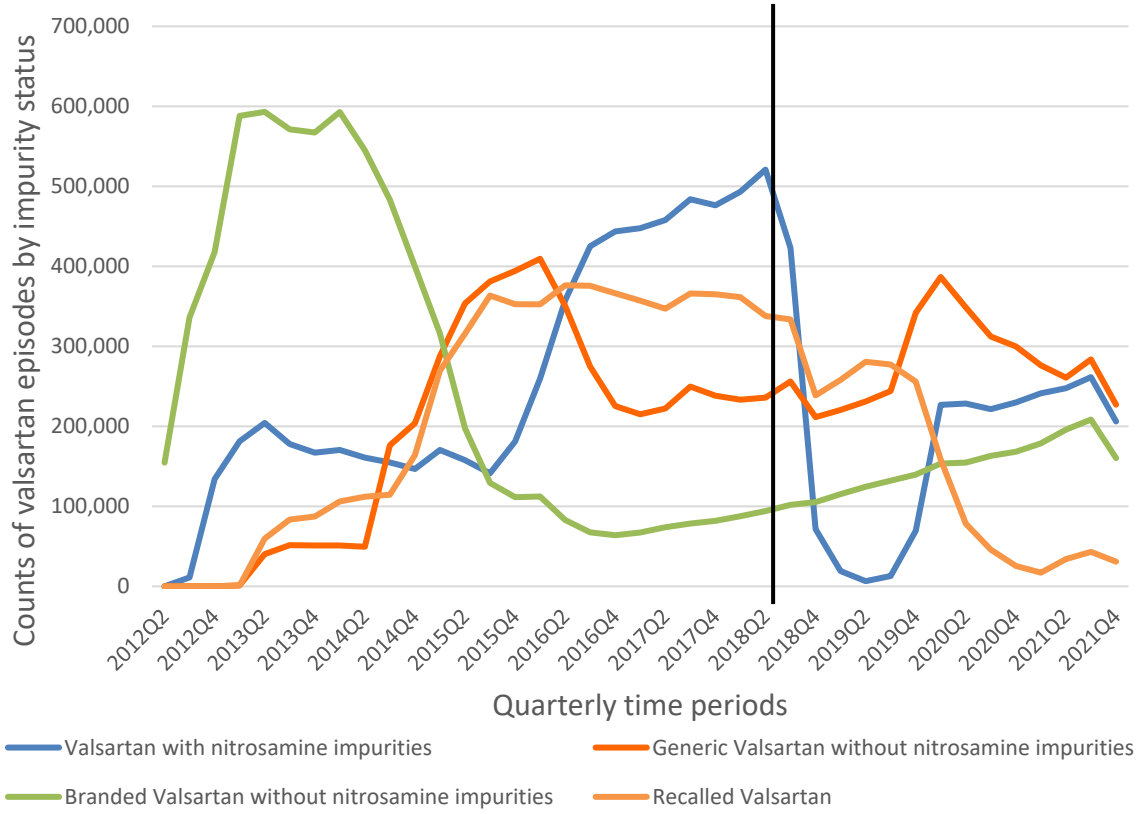
BMJ Open. 2023 Apr 17;13(4):e070985. doi: 10.1136/bmjopen-2022-070985.

Valsartan Utilization by Nitrosamine Impurity Status

Canada: Valsartan utilization by nitrosamine impurity status before and after valsartan recall notice



US: Valsartan utilization by nitrosamine impurity status before and after valsartan recall notice



Valsartan Episodes Duration by Nitrosamine Impurity Status, May 2012-December 2018

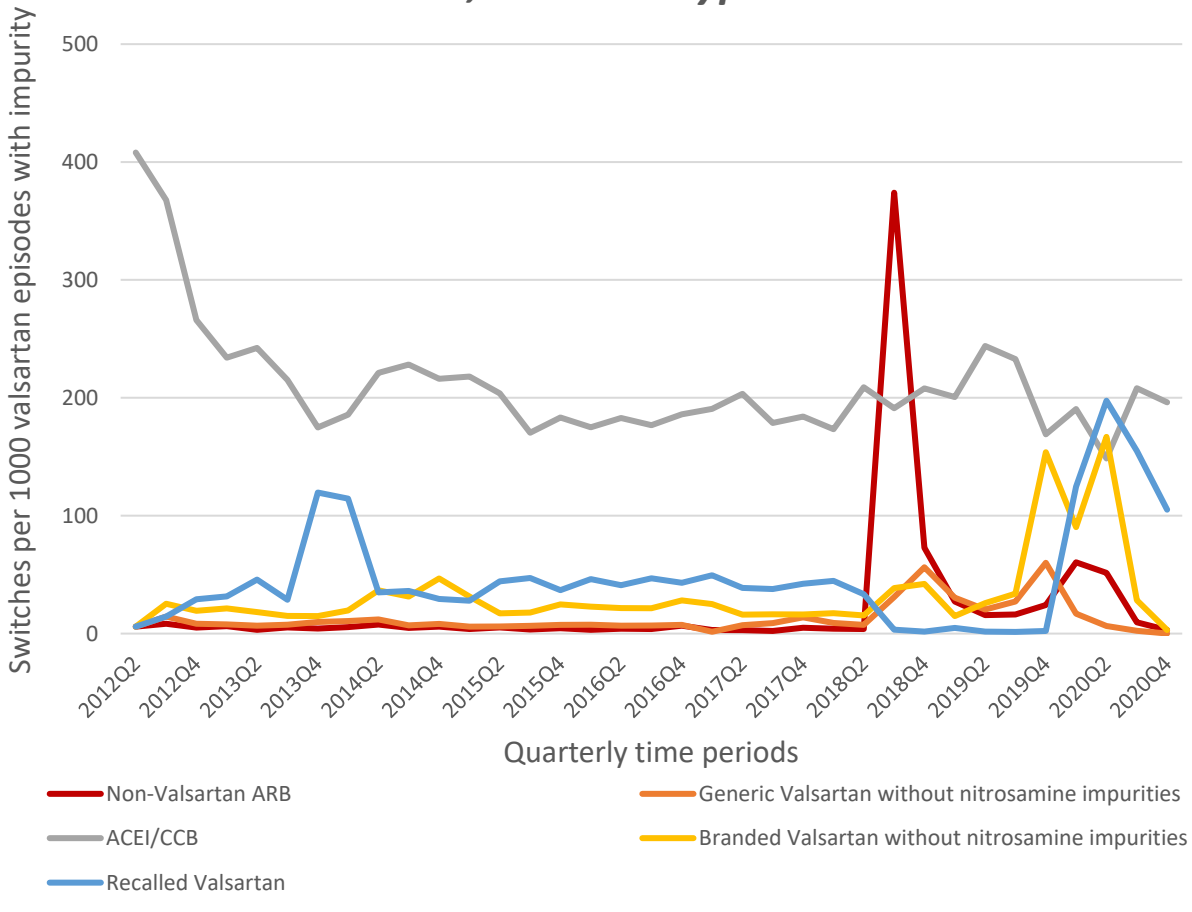
	US			Canada		
Valsartan Category	Total episodes (N)	Mean (days)	Median (days)	Total episodes (N)	Mean (days)	Median (days)
Nitrosamine Impurity	2,516,120	166.9	29-93	36786	145.4	48-69
Recalled	2,265,238	178.3	28-95	267355	269.0	104-121
Non-Recalled Generic	2,020,032	164.7	20-93	23106	146.7	61-85.5
Non-Recalled Branded	2,639,380	167.7	60-100	157863	319.2	98-120

Mean duration in US and Canada databases is an average of the episode duration across all data partners

- The mean duration of use of valsartan with nitrosamine impurity was around 5-6 months in the US and Canada. For the recalled valsartan products, duration of use was 178, 269 days in the US, Canada, respectively

Valsartan Switching Trends

Canada trends: Switching from valsartan with nitrosamine impurity to non-recalled valsartan, other ARBs, and anti-hypertensives



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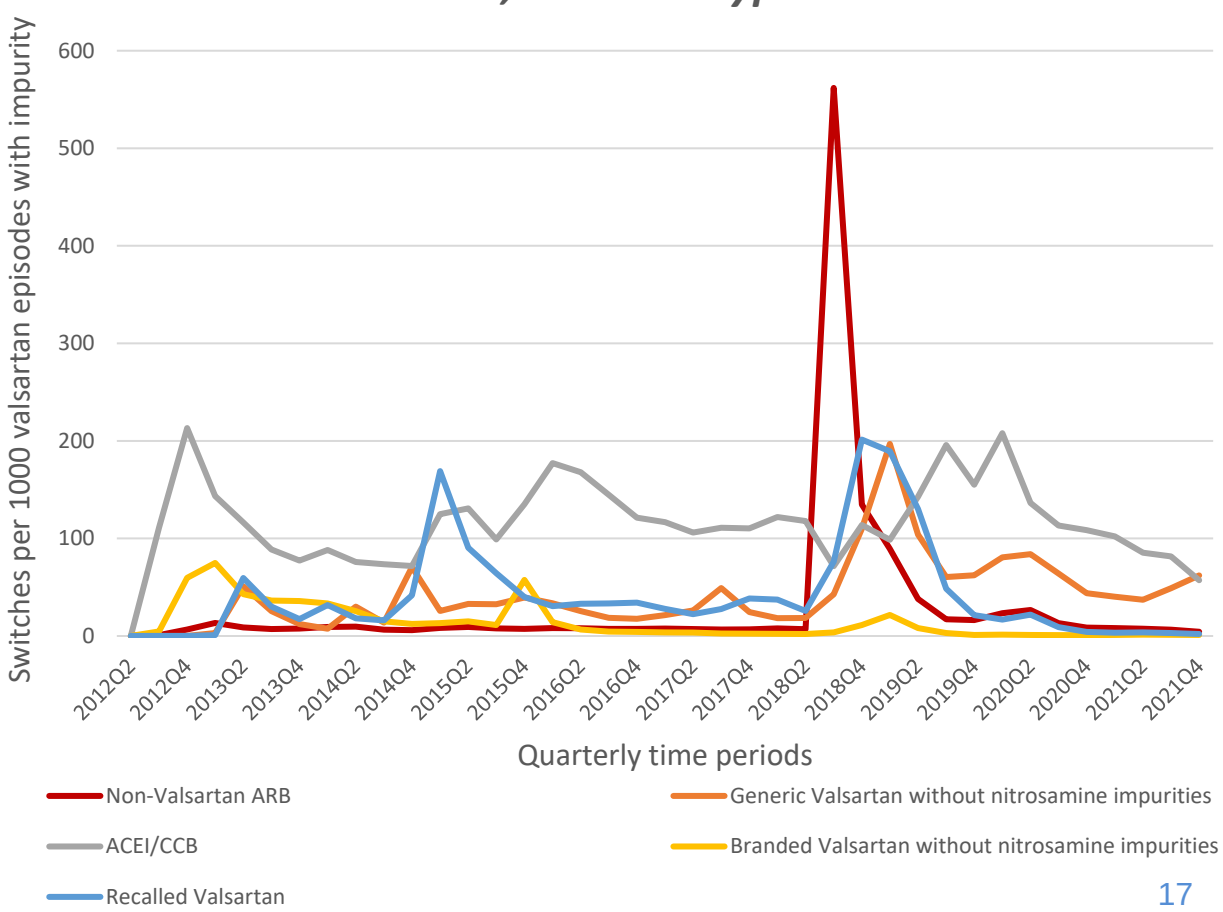

Summary

- Losartan is the most common ARB in the US, while it's candesartan in Canada
- Mean duration of recalled valsartan use was around 6 months in the US, and around 8 months in Canada
  - Based on the short duration of exposure, increased risk of cancer from nitrosamine impurities is unlikely.
- This example demonstrated the ability to utilize the Sentinel common data model in an international collaboration
- Allowed regulators to see the differing use patterns, but also areas of close similarity
- Demonstrates complementary systems – safety evaluations for products with low study power one country may be possible in others, to better inform the overall safety evaluation

Nitrosamine Research Team

Sentinel Operations Center

- Laura Hou
- Kimberly Barrett
- Christian Hague
- Ashish Rai
- Mayura Shinde
- Dan Scarnecchia
- Jennifer Thompson
- Samantha Smith
- Judith Maro

FDA

- Efe Eworuke
- Marie Bradley

CNODES (Canada)

- Michael Paterson
- Fangyun Wu

CPRD (U.K.)

- Rebecca Ghosh
- Stephen Welburn

SDU (Denmark)

- Peter Jensen
- Anton Pottegård

Sentinel

Nuts and Bolts: How North American Analyses in the Sentinel Common Data Model are Conducted

Judith Maro
Assistant Professor, Department of Population Medicine
Harvard Pilgrim Health Care Institute and Harvard Medical School

August 25, 2023

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https://www.sentinelinitiative.org

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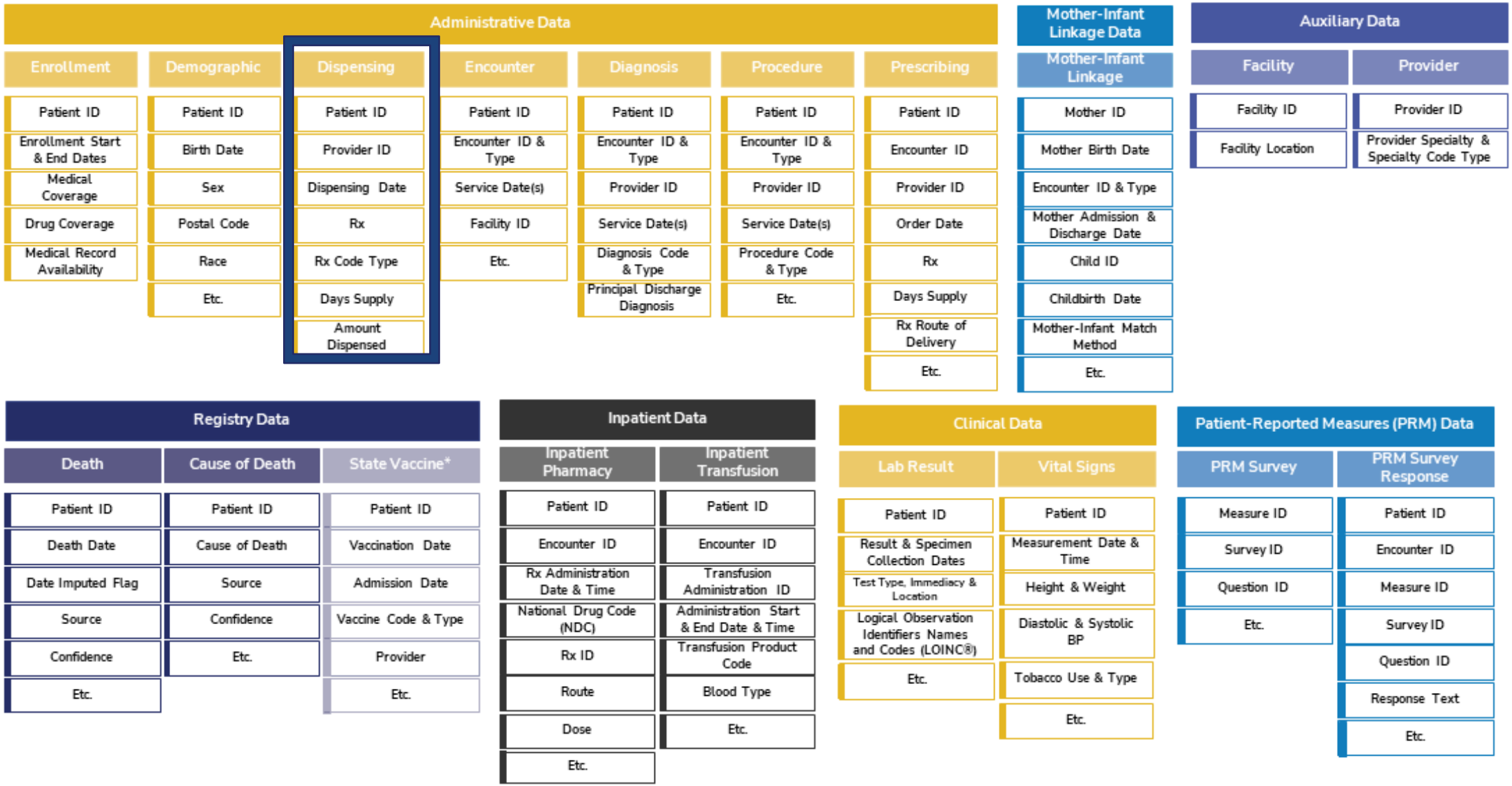
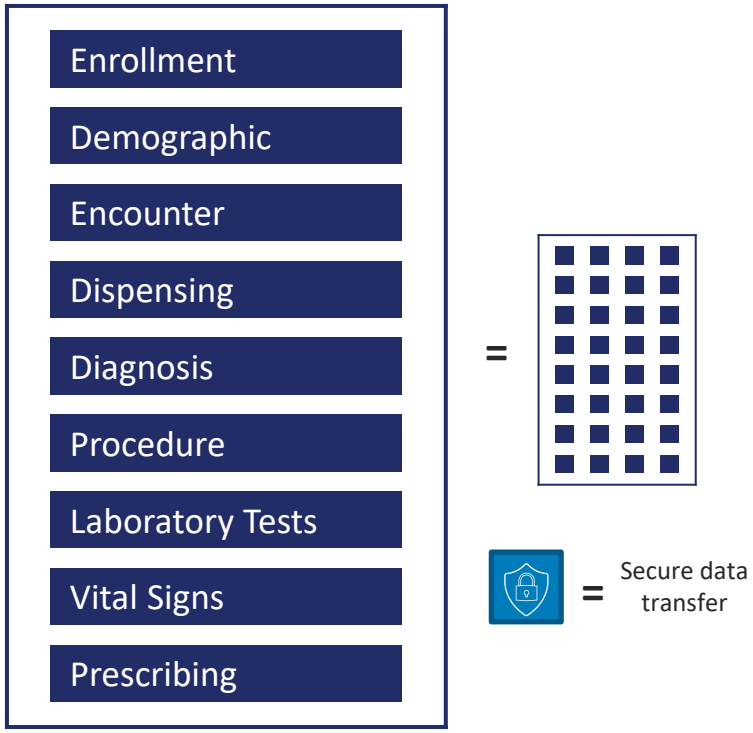


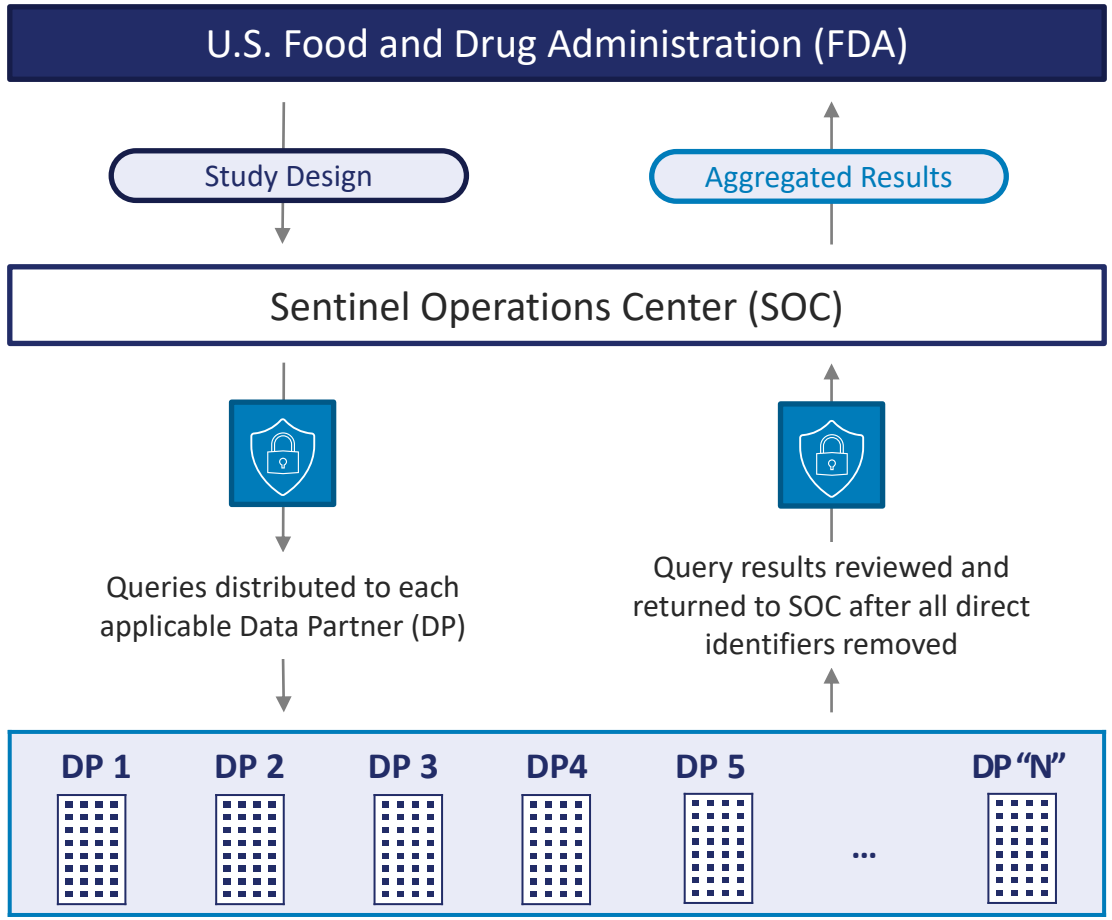
*The State Vaccine table has not been used since SCDM v6.0.

https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Sentinel Distributed Data Network (U.S.)

Data Partners (DPs) hold data in the Sentinel Common Data Model format

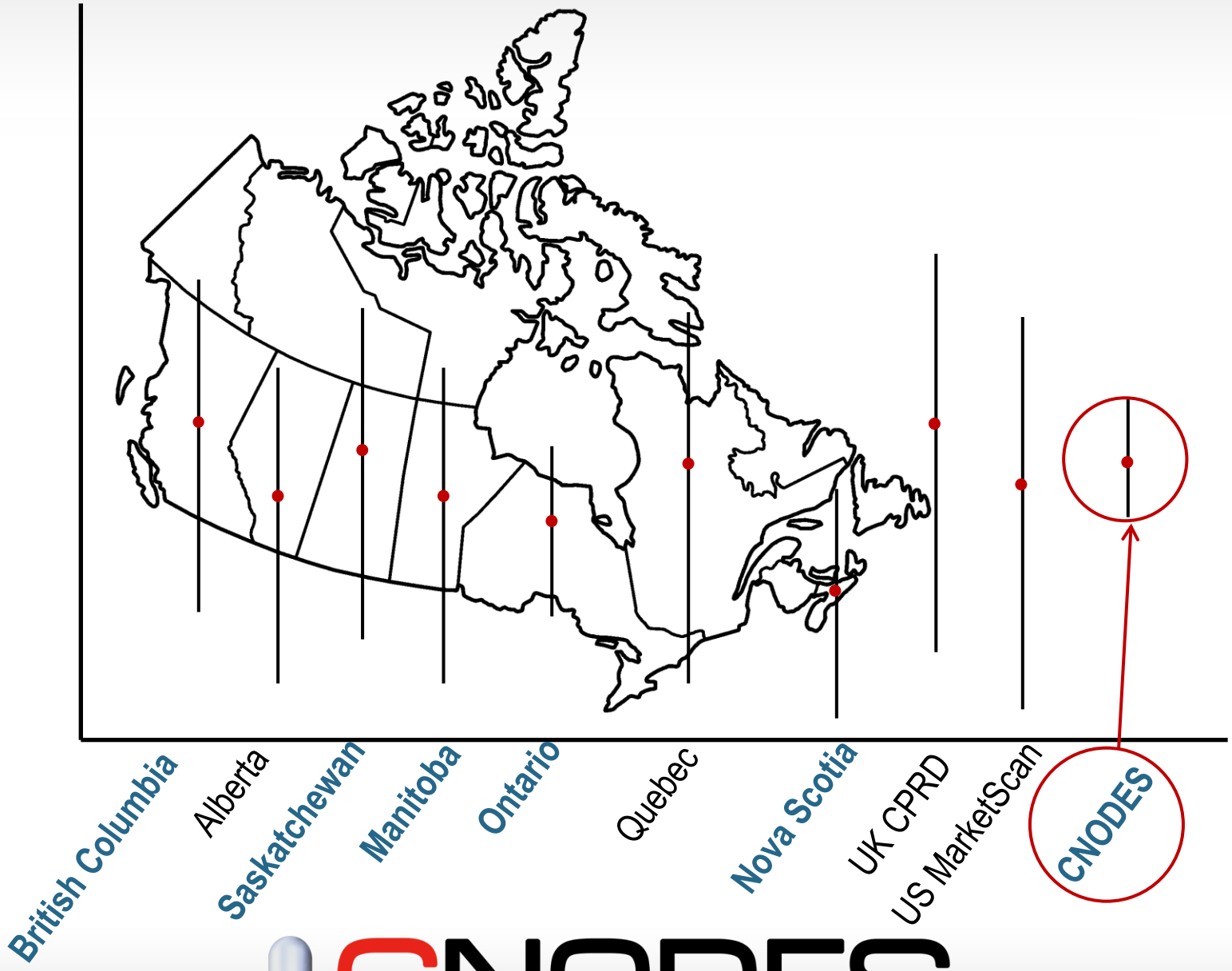




https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

CNODES Principal Investigators:
Robert Platt, Samy Suissa

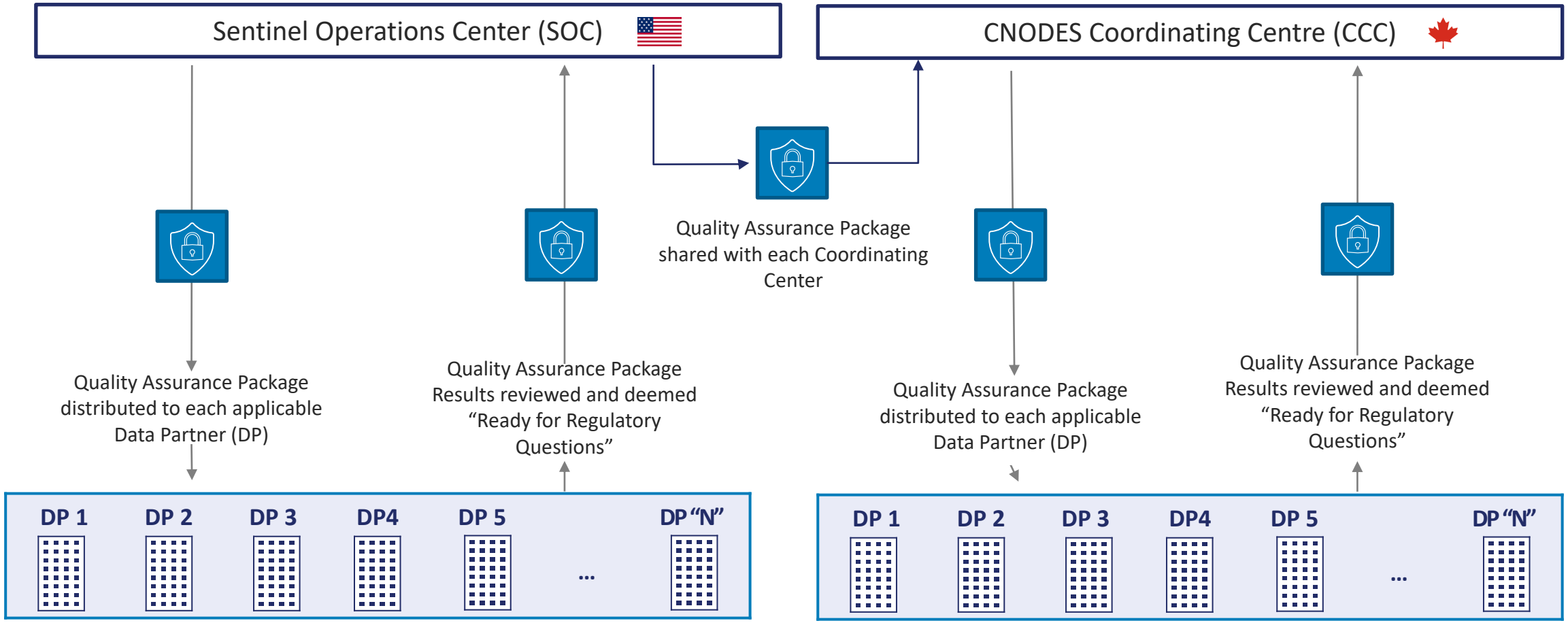
Data Sites with Common Data Model:
British Columbia, Saskatchewan, Manitoba, Ontario, Nova Scotia



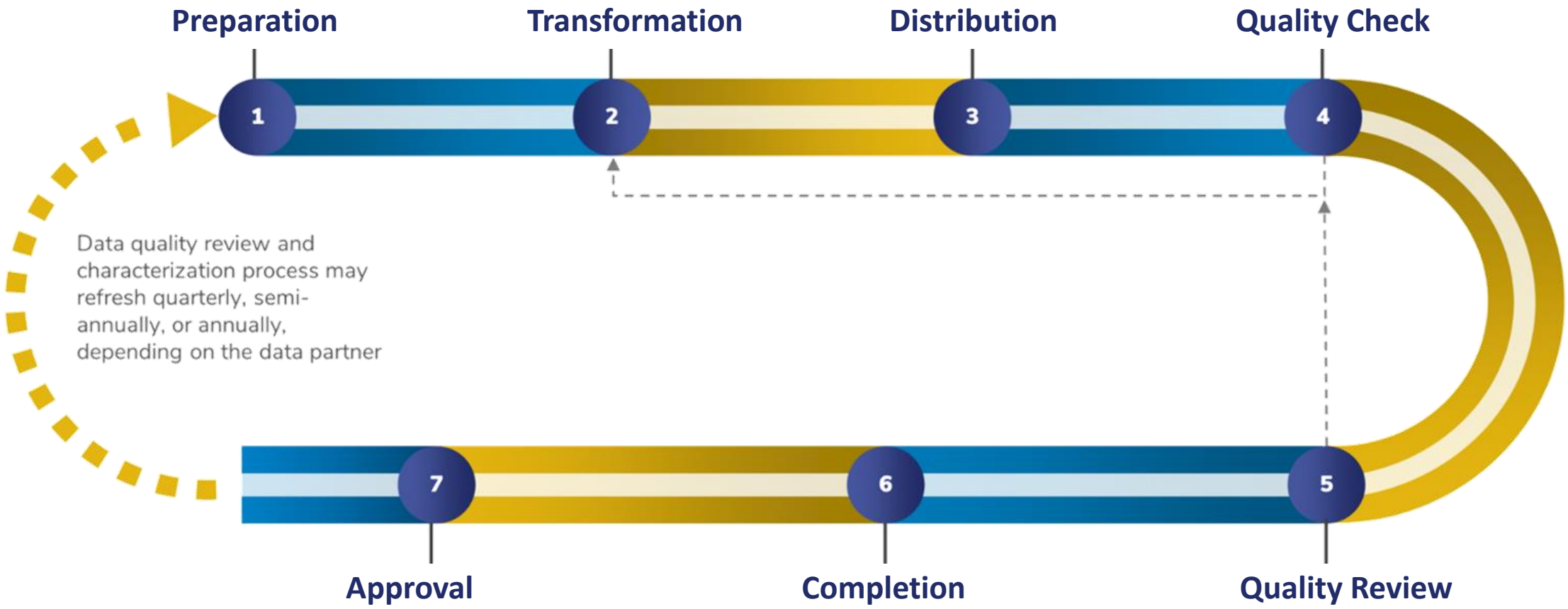
CNODES
CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES

https://www.cnodes.ca/

Quality Assurance in the Sentinel Distributed Data Network (U.S. and Canada)

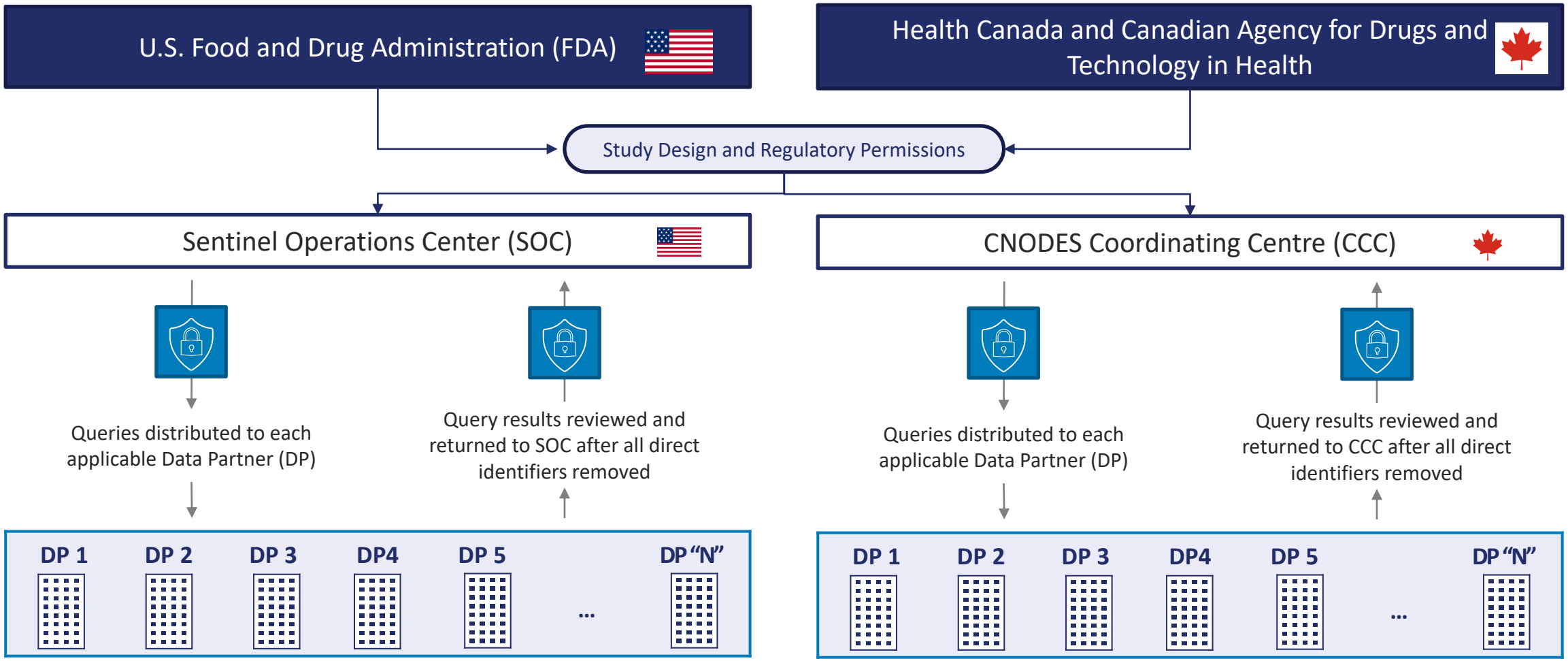


Data Quality Review and Characterization

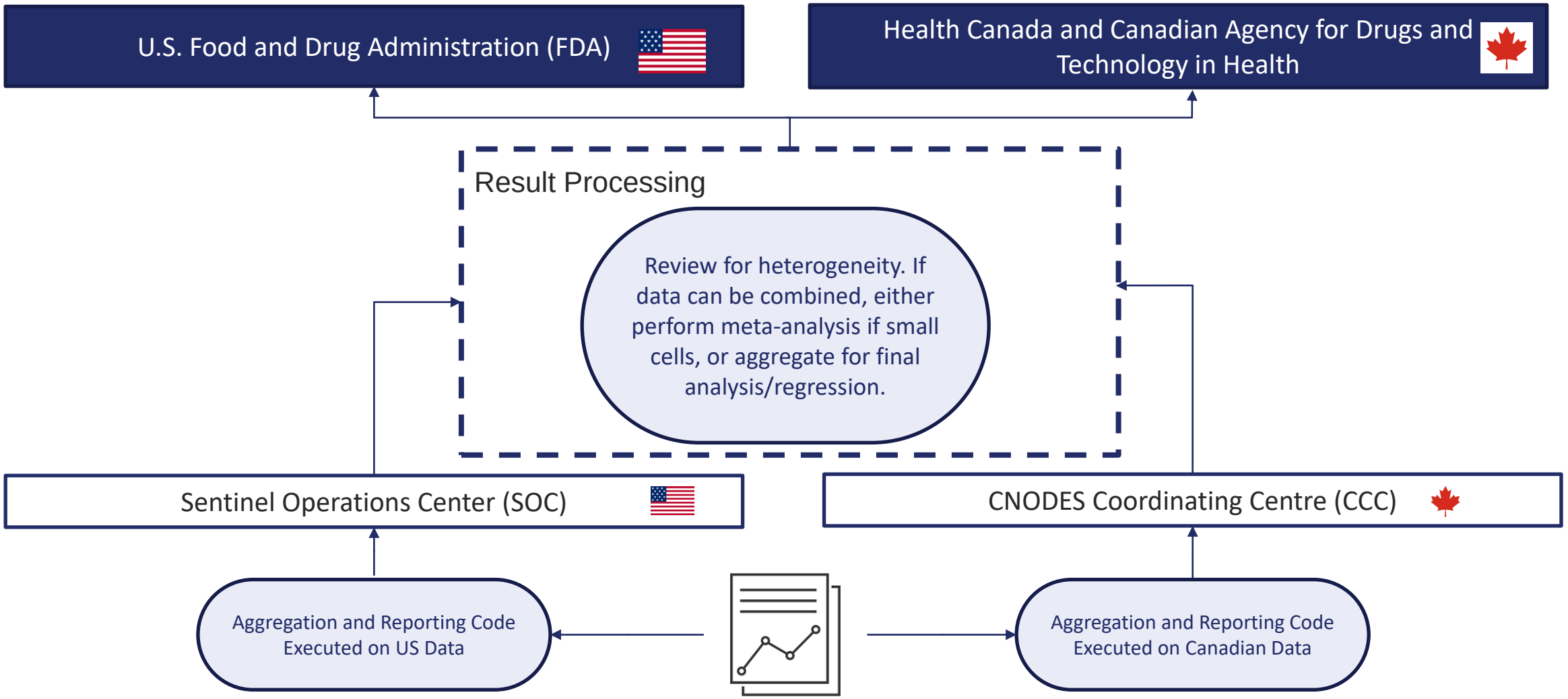


https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

Regulatory Queries in Sentinel Distributed Data Network (U.S. and Canada) – Step 1 (Distributed Code)



Regulatory Queries in Sentinel Distributed Data Network (U.S. and Canada) – Step 2 (Aggregation/Reporting Code)



Be Transparent about Heterogeneity and Make Informed Decisions About Combining Data

Table 1 Selected demographic and clinical characteristics for all Angiotensin-Receptor-Blockers displayed by country

Characteristics	USA (%)	Canada (%)	Denmark (%)	UK (%)
Number of ARB users	10 836 991	1 775 080	1 153 841	3 270 823
Number of episodes*	22 406 719	798 231	492 229	578 652
Individual ARB episodes				
Azilsartan	0.6	–	–	0.005
Candesartan	0.9	27.5	4.8	34.2
Eprosartan	0.006	–	–	0.4
Irbesartan	5.2	18.3	0.6	10.2
Losartan	67.9	11.4	93.5	48.3
Olmesartan	8.6	12.2	–	2.3
Telmisartan	2.2	21.1	0.4	1.9
Valsartan	18.4	16.3	1.0	3.1
Age				
18–44 years	5.5	3.5	5.6	3.6
45–64 years	25.8	17.6	39.1	32.8
≥65 years	68.7	78.9	55.3	63.7
Gender				
Female	55.9	54.5	51.4	53.5
Male	44.1	45.5	48.6	46.5

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10111915/pdf/bmjopen-2022-070985.pdf

Sentinel Regulatory Queries Published Online

Analytic Request Packages Available for Download

Request ID	Summary
cder_sir_wp004	Outcome Monitoring following Erenumab Use: A Signal Identification Analysis
cder_mpl2p_wp032	Angioedema following Sacubitril/Valsartan Use in Patients with Heart Failure: An Updated Propensity Score Analysis
cder_mpl2r_wp019	Mortality Following Long-Acting Injectable Antipsychotics Use in Patients with Dementia: An Inverse Probability of Treatment Weighting Analysis
cder_mpl2p_wp033	Racial Differences in COVID-19 Outcomes (2020-2021)
cder_sir_wp005	Outcome Monitoring Following Zarxio Use: An Updated Signal Identification Analysis
cder_mpl1p_wp072	Congenital Malformations Observed in the Mother's Records Following Fingolimod Use During Pregnancy: A Descriptive Analysis
cder_mpl1p_wp063	Congenital Malformations Observed in the Mother's or Linked Infant's Records Following Fingolimod Use During Pregnancy: A Descriptive Analysis
cder_mpl1r_wp228	Cardiovascular Outcomes Following Percutaneous Transluminal Septal Myocardial Ablation (PTSMA) Procedures: A Descriptive Analysis
cder_mpl1r_wp240	Cardiovascular Outcomes Following Percutaneous Transluminal Septal Myocardial Ablation (PTSMA) Procedures: An Updated Descriptive Analysis (a follow-up to cder_mpl1r_wp228)
cder_sir_wp003	Outcome Monitoring Following Zarxio Use: A Signal Identification Analysis
cder_sir_wp002	Outcome Monitoring Following Ozempic Use in Patients with Type 2 Diabetes: A Signal Identification Analysis
cder_mpl2p_wp024	Fractures following Leuprolide Acetate Use: A Multiple Factor Matched Analysis (a follow-up to cder_mpl2p_wp011)
cder_mpl2p_wp011	Fractures following Leuprolide Acetate Use: A Multiple Factor Matched Analysis
cder_mpl2r_wp007	Seizures following Gadolinium-Based Contrast Agents Exposure: A Self-Controlled Risk Interval Analysis
cder_mpl2p_wp029	Characterizing Pregnant Women With and Without Evidence of Heart Failure and Non-Pregnant Women With Heart Failure: A Propensity Score Matched Analysis
cder_mpl2p_wp028	Thromboembolic Stroke, Major Extracranial Bleeding, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Direct Oral Anticoagulant Use: An Inverse Probability of Treatment Weighting Analysis

https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse

“How to” Collaboration Takeaways

- **Context and local expertise matters.** Leverage the subject matter expertise in each country/jurisdiction to ensure that we are measuring or quantifying the same medical concepts especially when using heterogeneous coding systems.

- **Embrace wanted/desired heterogeneity** from country-specific results while eliminating unwanted heterogeneity from different programming approaches. Present country-specific data and use deliberate decision-making for further combining.

- **Regulatory compliance rules are complicated.** Start early to establish routine practices and procedures that will allow analysis methodologies that abide by each country’s privacy and security regulations.

Discussion / Questions