



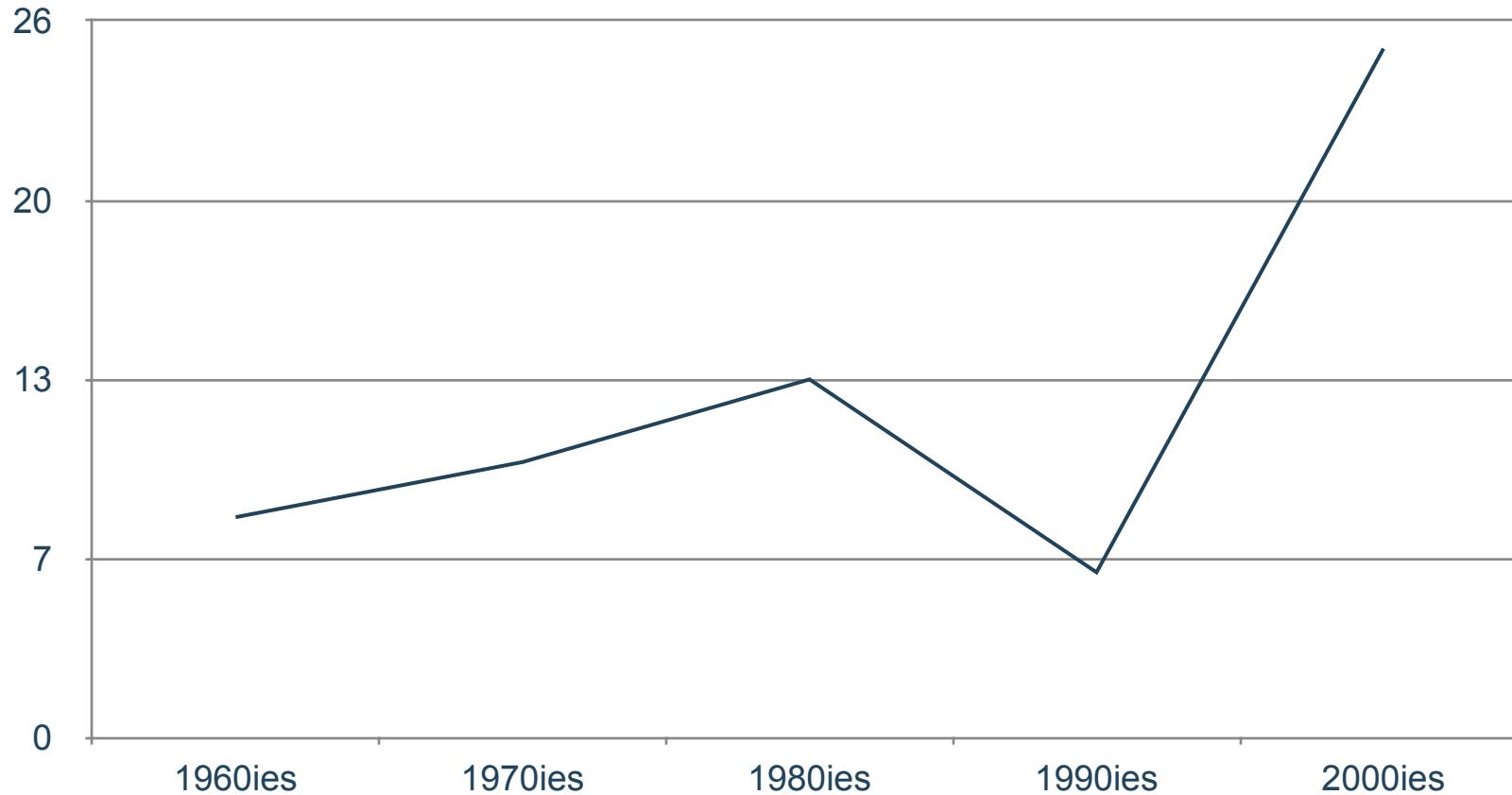
# Von Real-World-Data zu Evidenz Die Vision von OHDSI

Ines Reinecke, [ines.reinecke@ukdd.de](mailto:ines.reinecke@ukdd.de)  
DIZ Leitung, Universitätsklinikum Carl Gustav Carus Dresden

19. Dezember 2023

# FDA Regulatory Action over Time

## Number of FDA-caused Withdrawals



# FDAAA calls for establishing Risk Identification and Analysis System

Observational  
Medical  
Outcomes  
Partnership

## SEC. 905. ACTIVE POSTMARKET RISK IDENTIFICATION AND ANALYSIS.

(a) IN GENERAL.—Subsection (k) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended by adding at the end the following:

“(3) ACTIVE POSTMARKET RISK IDENTIFICATION.—

“(A) DEFINITION.—In this paragraph, the term ‘data’ refers to information with respect to a drug approved under this section or under section 351 of the Public Health Service Act, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

“(B) DEVELOPMENT OF POSTMARKET RISK IDENTIFICATION AND ANALYSIS METHODS.—The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—

“(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

“(ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

“(I) at least 25,000,000 patients by July 1, 2010; and

“(II) at least 100,000,000 patients by July 1, 2012; and

“(iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

“(C) ESTABLISHMENT OF THE POSTMARKET RISK IDENTIFICATION AND ANALYSIS SYSTEM.—



## The Sentinel Initiative

National Strategy for Monitoring Medical Product Safety

May 2008



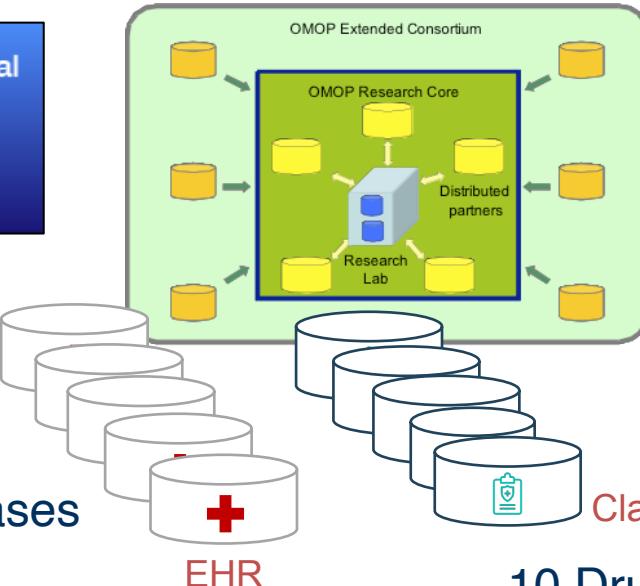
FDA

## Risk Identification and Analysis System:

a systematic and reproducible process to efficiently generate evidence to support the characterization of the potential effects of medical products from across a network of disparate observational healthcare data sources

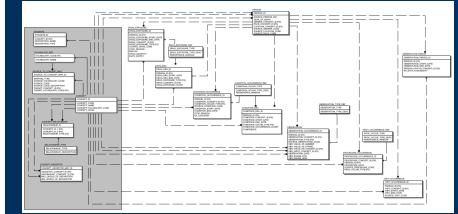
# OMOP Experiment

Observational  
Medical  
Outcomes  
Partnership

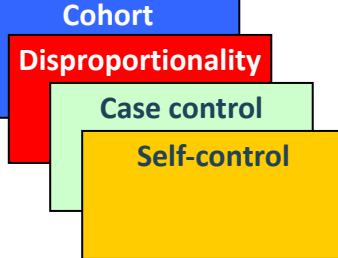


- Open-source
- Standards-based

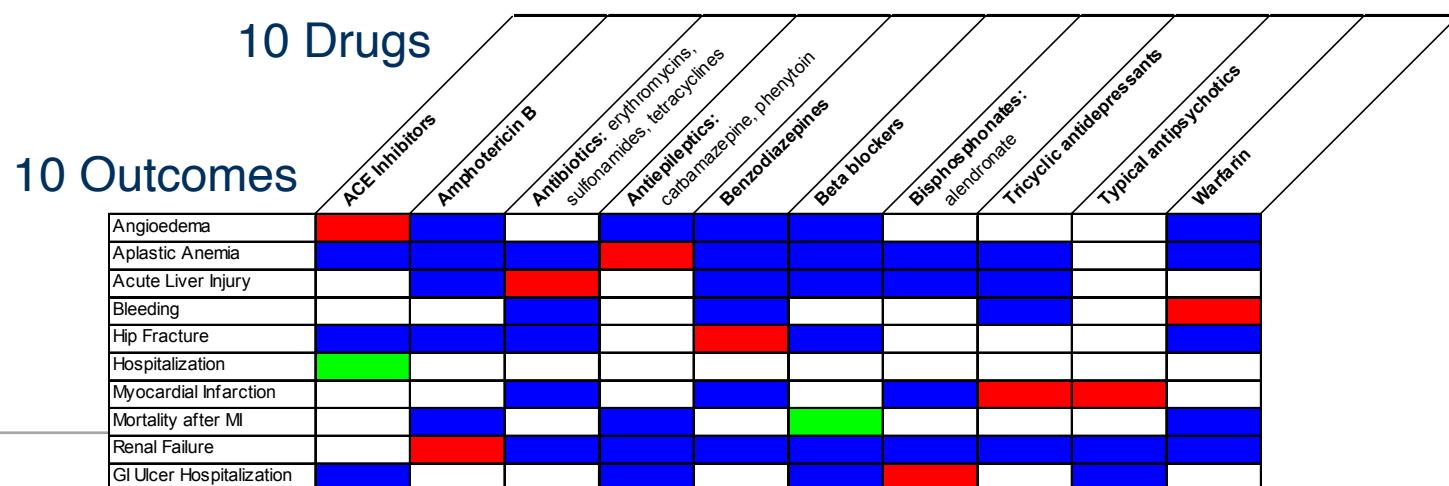
Common Data



## OMOP Methods Library



- 14 methods \* 70 settings = 1,000 SAS scripts



## Main findings in OMOP experiment

### Heterogeneity in Estimates

due to choice of **databases** and **analysis methods**

**“NO REAL WORLD EVIDENCE”**

# Observational research crisis

ORIGINAL CONTRIBUTION

**JAMA**

## Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Chris R. Cardwell, PhD  
Christian C. Abnet, PhD  
Marie M. Cantwell, PhD  
Liam J. Murray, MD

**DISPHOSPHONATES INHIBIT OSTEOCLAST-MEDIATED BONE RESORPTION**

**August 2010: "Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer"**

sembles ground alendronate tablets has been found on biopsy in patients with bisphosphonate-related esophagitis, and follow-up endoscopies have shown that abnormalities remain after the esophagitis heals.<sup>6</sup> Reflux esophagitis is an established risk factor for esophageal cancer through the Barrett pathway.<sup>7-9</sup> It is not known whether bisphosphonate-related esophagitis can also increase esophageal cancer risk. However, the US Food and Drug Administration recently reported 23 cases of esophageal cancer (between 1995 and 2008) in patients using the bisphosphonate alendronate and a further 31 cases in patients using bisphosphonates other than alendronate.

**Context** Use of oral bisphosphonates has increased dramatically and elsewhere. Esophagitis is a known adverse effect of oral bisphosphonates, but recent reports suggest a link between bisphosphonate use and esophageal cancer that has not been robustly investigated.

**Objective** To investigate the association between bisphosphonate use and esophageal and gastric cancer.

**Design, Setting, and Participants** Data were extracted from the UK General Practice Research Database, a prospective, observational study of general practices in the United Kingdom. The study included all patients aged 16 years or older who were registered with a general practice in the United Kingdom and had a prescription for oral bisphosphonates between January 1, 1995, and December 31, 2008. The study included all patients aged 16 years or older who were registered with a general practice in the United Kingdom and had a prescription for oral bisphosphonates between January 1, 1995, and December 31, 2008.

**Exposures** Use of oral bisphosphonates.

**Outcomes and Measures** Incident cases of esophageal and gastric cancer were identified through the General Practice Research Database and the National Cancer Registry.

**Interventions** Use of oral bisphosphonates.

**Statistical Analysis** Cox proportional hazard regression analysis was used to estimate the hazard ratio for esophageal and gastric cancer.

**Results** A total of 10 641 patients were included in the study. The mean age was 60.7 years (range, 16-95 years). The mean duration of bisphosphonate use was 3.5 years (range, 0-15 years). The hazard ratio for esophageal cancer was 1.0 (95% confidence interval, 0.9-1.1). The hazard ratio for gastric cancer was 1.0 (95% confidence interval, 0.9-1.1). There was no significant association between bisphosphonate use and esophageal or gastric cancer.

**Conclusion** Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with esophageal or gastric cancer.

*JAMA. 2010;304(6):657-663*

**Large studies with appropriate comparison groups, adequate follow-up, robust characterization of bisphosphonate use, and appropriate adjustment for confounding factors are needed to determine whether bisphosphonate use increases esophageal cancer risk.**

**RESEARCH**

**BMJ**

## Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,<sup>1</sup> Gabriela Czanner, statistician,<sup>1</sup> Gillian Reeves, statistical epidemiologist,<sup>1</sup> Joanna Watson, epidemiologist,<sup>1</sup> Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,<sup>2</sup> Valerie Beral, professor of cancer epidemiology<sup>1</sup>

**ABSTRACT**

**Objective** To examine the hypothesis that risk of oesophageal, but not of gastric or colorectal, cancer is increased in users of oral bisphosphonates.

**Design** Nested case-control analysis within a primary care cohort of about 6 million people in the UK, with prospectively recorded information on prescribing of bisphosphonates.

**Setting** UK General Practice Research Database cohort.

**Participants** Men and women aged 40 years or over—2954 with oesophageal cancer, 2018 with gastric cancer, and 10 641 with colorectal cancer, diagnosed in 1995–2005; five controls per case matched for age, sex, general practice, and observation time.

**Main outcome measures** Relative risks for incident invasive cancers of the oesophagus, stomach, and colorectum, adjusted for smoking, alcohol, and body mass index.

**Conclusions** The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal cancer at age 60–79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

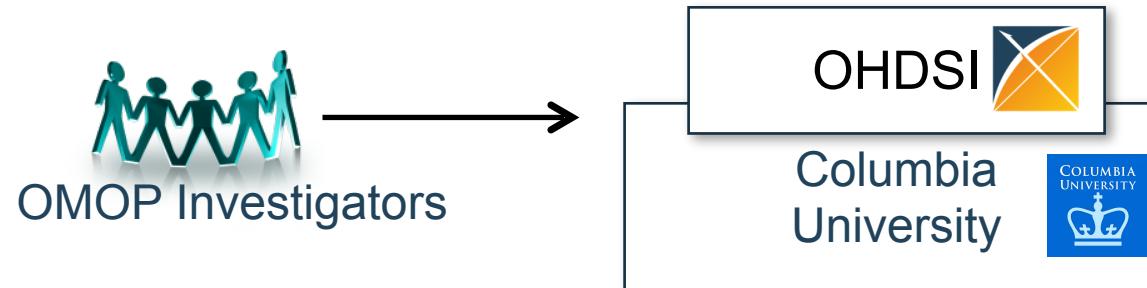
**INTRODUCTION**

Adverse gastrointestinal effects are common among people who take oral bisphosphonates for the prevention and treatment of osteoporosis; they range from dyspepsia, nausea, and abdominal pain to erosive oesophagitis and oesophageal ulcers.<sup>1</sup> Recent case reports have suggested a possible increase in the risk of oesophageal cancer with use of such bisphosphonate preparations.<sup>2</sup> We report here on the relation between prospectively recorded prescribing information for

**Sept 2010: "In this large nested case-control study within a UK cohort [General Practice Research Database], we found a significantly increased risk of oesophageal cancer in people with previous prescriptions for oral bisphosphonates"**

Quelle: <https://www.ohdsi.org/wp-content/uploads/2019/09/Medinfo-OHDSI-Hripcak-2019.pdf>

# OMOP to OHDSI



The Observational Health Data Sciences and Informatics (OHDSI) program is a **multi-stakeholder, interdisciplinary collaborative** to create **open-source** solutions that bring out the value of observational health data through large-scale analytics

OHDSI has established an **international network of researchers and observational health databases** with a central coordinating centre housed at Columbia University



Public, open



Not pharma funded



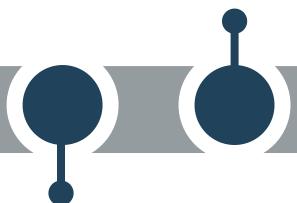
International

# History of OMOP/OHDSI

## OMOP Experiment #2/ European OMOP

- Focused on a subset of data (4 claims, 1 EHR) and 7 methods
- Replicating experiment findings on European databases

2011



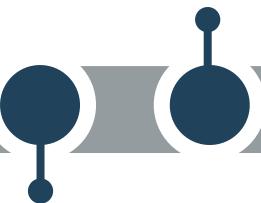
## OMOP Experiment #1

- FDAAA calls for establishing Risk Identification and Analysis System for drug surveillance
- OMOP Experiment creates a framework for evaluating 14 methods of epidemiological designs
- 10 data sources, claims and EHRs, 200M+ lives

## Launch of OHDSI

- OHDSI's first face-to-face meeting at Columbia University

2014

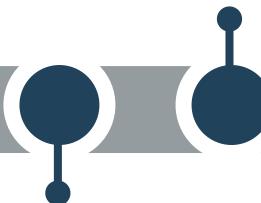


## Formation of China Chapter

- To use data science and informatics methods to promote health and medical data research in China

## Formation of Korea Chapter

2016



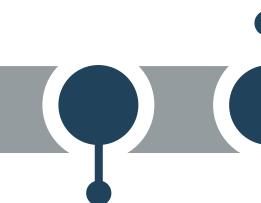
## EHDEN Initiation (Europe)

- Started under the Innovative Medicines Initiative (IMI) that will drive the adoption of the OMOP-CDM in Europe

## FederNET Initiation (Korea)

## First European Symposium

2018

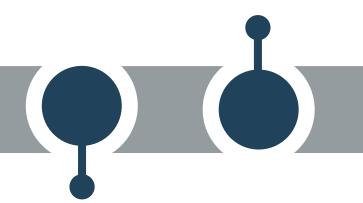


## NMPA Adoption

## Global Acceptance

- OHDSI grows to >152 databases, 18 countries, 2.1B patient records, 369M ex-US
- Regional chapters in US, Europe, China, South Korea + Asia-Pacific, Latin America
- Offering regional symposia

2020



2019

## EMA Adoption

## Formation of Australia, Japan and Singapore Chapters

2015

## First OHDSI Symposium/ Network Study Published

- Community begins open source work under OHDSI brand
- First global network study characterizing treatment pathways

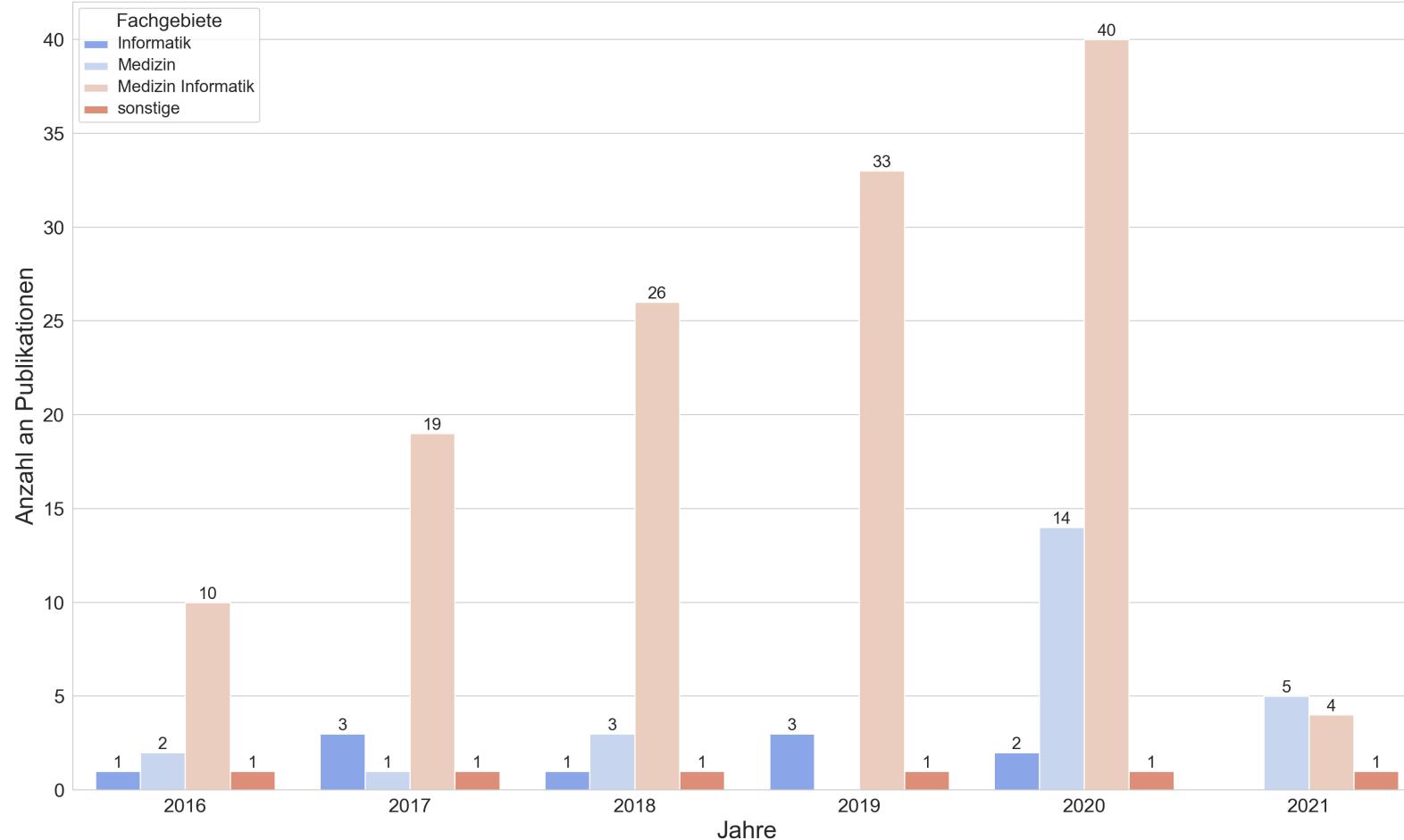
## First Hackathon at Columbia University

## Formation of European Chapter

- Led by the coordinating center at the Erasmus University Medical Center in Rotterdam

## FDA Adoption (FDA BEST Launch)

# The usage of OMOP/OHDSI - Scoping Review



# OHDSI Network Studies - Data Elements Analysis

Publikation - OHDSI Studien	Diagnose	Medikation	Laborwerte	Prozeduren	Beobachtungen	Scores
Hripcak, George et al., 2016	*	*				
Samwald, Matthias et al., 2016	*	*				
Duke, Jon D. et al., 2017	*	*				
Boland, Mary Regina et al., 2018	*	*	*	*	*	*
Vashisht, Rohit et al., 2018	*	*				
Zhang, Xin et al., 2018	*	*				
Kubota, Kiyoshi et al., 2018	*	*				
Viernes, Benjamin et al., 2019	*	*				
Brauer, Ruth et al., 2020	*	*				
Seo, Seung In et al., 2020	*	*				*
Spotnitz, Matthew E. et al., 2020	*	*		*		
Chen, Ruijun et al., 2020	*	*	*			
Hripcak, George et al., 2020	*	*	*	*	*	*
Choi, Youn I. et al., 2020	*	*	*			
Chandler, Rebecca E. et al., 2020	*	*				
Kim, Hunmin et al., 2020	*	*				
Kim, Yeesuk et al., 2020	*	*				
Brat, Gabriel A. et al., 2020	*		*			
Lane, Jennifer C.E. et al., 2020	*	*			*	*
Burn, Edward et al., 2020a	*	*				
You, Seng Chan et al., 2020	*	*	*	*		
Burn, Edward et al., 2020b	*			*		
Amutha, Anandakumar et al., 2021	*	*	*			
Hockett, Christine W. et al., 2021	*		*			
Morales, Daniel R. et al., 2021	*	*				
Lane, Jennifer C. E. et al., 2021	*	*	*	*		
Jensen, Elizabeth T. et al., 2021	*	*				
Kim, Ha Il et al., 2021	*				*	

# OHDSI Network Studies - Data Elements Analysis

## Publikation - OHDSI Studien

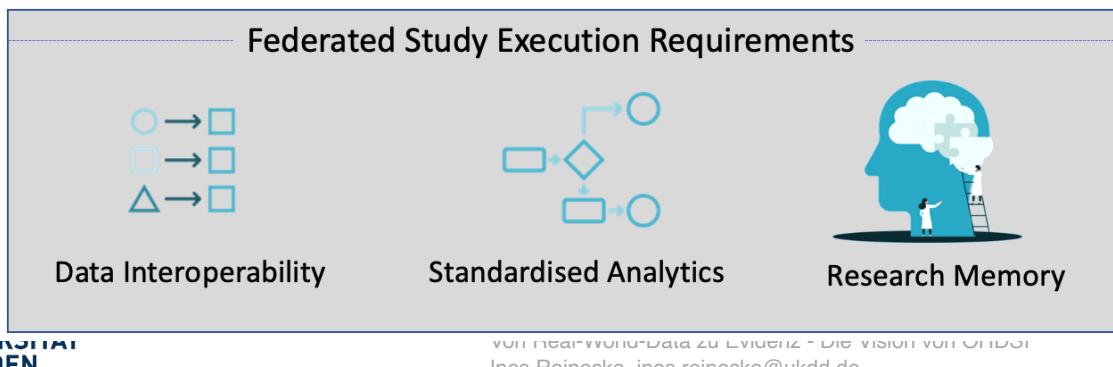
Hripcak, George et al., 2016  
Samwald, Matthias et al., 2016  
Duke, Jon D. et al., 2017  
Boland, Mary Regina et al., 2018  
Vashisht, Rohit et al., 2018  
Zhang, Xin et al., 2018  
Kubota, Kiyoshi et al., 2018  
Viernes, Benjamin et al., 2019  
Brauer, Ruth et al., 2020  
Seo, Seung In et al., 2020  
Spotnitz, Matthew E. et al., 2020  
Chen, Ruijun et al., 2020  
Hripcak, George et al., 2020  
Choi, Youn I. et al., 2020  
Chandler, Rebecca E. et al., 2020  
Kim, Hunmin et al., 2020  
Kim, Yeesuk et al., 2020  
Brat, Gabriel A. et al., 2020  
Lane, Jennifer C.E. et al., 2020  
Burn, Edward et al., 2020a  
You, Seng Chan et al., 2020  
Burn, Edward et al., 2020b  
Amutha, Anandakumar et al., 2021  
Hockett, Christine W. et al., 2021  
Morales, Daniel R. et al., 2021  
Lane, Jennifer C. E. et al., 2021  
Jensen, Elizabeth T. et al., 2021  
Kim, Ha Il et al., 2021

## Themen

Characterizing treatment pathways at scale using the OHDSI network  
Incidence of Exposure of Patients in the United States to Multiple Drugs for Which Pharmacogenomic Guidelines Are Available.  
Risk of angioedema associated with levetiracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network.  
Uncovering exposures responsible for birth season - disease effects: a global study.  
Association of Hemoglobin A1c Levels With Use of Sulfonylureas, Dipeptidyl Peptidase 4 Inhibitors, and Thiazolidinediones in Patients With Type 2 Diabetes Treated With Analysis of treatment pathways for three chronic diseases using OMOP CDM.  
Penetration of new antidiabetic medications in East Asian countries and the United States: A cross-national comparative study.  
Characterizing VA Users with the OMOP Common Data Model.  
Application of a Common Data Model (CDM) to rank the paediatric user and prescription prevalence of 15 different drug classes in South Korea, Hong Kong, Taiwan, Japan and  
Comparative risk of Clostridium difficile infection between proton pump inhibitors and histamine-2 receptor antagonists: A 15-year hospital cohort study using a common data  
Relative Risk of Cervical Neoplasms Among Copper and Levonorgestrel-Releasing Intrauterine System Users.  
Treatment Patterns for Chronic Comorbid Conditions in Patients With Cancer Using a Large-Scale Observational Data Network.  
Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension.  
Effect of Age on the Initiation of Biologic Agent Therapy in Patients With Inflammatory Bowel Disease: Korean Common Data Model Cohort Study.  
Nintedanib and ischemic colitis: Signal assessment with the integrated use of two types of real-world evidence, spontaneous reports of suspected adverse drug reactions, and  
Characterization of Anti-seizure Medication Treatment Pathways in Pediatric Epilepsy Using the Electronic Health Record-Based Common Data Model.  
Comparative safety and effectiveness of alendronate versus raloxifene in women with osteoporosis.  
International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium.  
Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study.  
An international characterisation of patients hospitalised with COVID-19 and a comparison with those previously hospitalised with influenza.  
Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention.  
Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study.  
Treatment regimens and glycosylated hemoglobin levels in youth with Type 1 and Type 2 diabetes: Data from SEARCH (United States) and YDR (India) registries.  
Clinical profile at diagnosis with youth-onset type 1 and type 2 diabetes in two pediatric diabetes registries: SEARCH (United States) and YDR (India).  
Renin-angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis.  
Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multinational network cohort study.  
Comparison of the incidence of diabetes in United States and Indian youth: An international harmonization of youth diabetes registries.  
Gastrointestinal and Nongastrointestinal Complications of Esophagogastroduodenoscopy and Colonoscopy in the Real World: A Nationwide Standard Cohort Using OMOP CDM

# Data Analysis and Real World Interrogation Network (DARWIN)

- EMA announced DARWIN in 2021
- DARWIN EU coordination center - Erasmus University Medical Center Rotterdam
- Goal: „By 2025 the use of Real World Evidence will have been enabled and the value will have been established across the spectrum of regulatory use case“
- Data partner onboarding is ongoing – phase 2
- Paradigm shift, shift for fast delivery of reliable evidence for regulatory decision making on the utilization, safety and effectiveness of medical products throughout their lifecycle
- Strong focus on methodology and standardized analytics



<https://www.darwin-eu.org/index.php/methods>



### Idea:

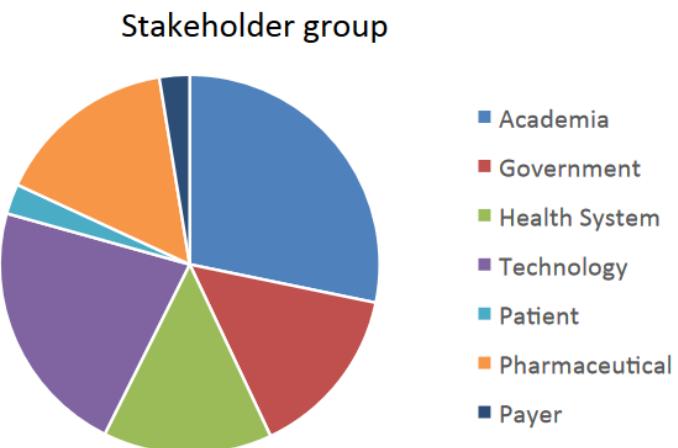
- Studying Drug shortages in Europe: A Multinational, Multidatabase Network Study
- Drug shortage in Europe
- Idea to have all EHDEN datapartners participating in this study
- Goal is a better understanding of drug shortage in routine health care delivery, including indication, treatment duration, doses and trends

### Background:

- Since 2016, EMA publishes a public catalogue of medicines under surveillance due to shortage in more than one European country.
- Activities temporarily suspended between March 2020 and December 2021 due to the COVID-19 pandemic.
- EMA published a list of critical medicines for Covid-19 public health emergency.
-

## What OHDSI is:

- ✓ Open Source
- ✓ Community
- ✓ Data



### OHDSI Collaborators:

- 2,100 users
- 25 workgroups
- 20 open-source applications

### OHDSI Network:

- >160+ databases
- 23 countries
- 578M distinct patients
- 2.7B de-identified patient records

# OHDSI Community Activities

  
OHDSI workgroups  
<https://www.ohdsi.org/workgroups/>

  
FHIR and OMOP  
Current Participants: 287  
Leads: Jon Duke, Davra Gabriel, Christian Reich

Registry  
Current Participants: 175  
Lead: Tina Parciak

2023 OKRs

## OHDSI Symposium - worldwide - Europe - APAC



## OHDSI Europe team European Country Chapters - OHDSI Germany



Von Real-World-Data zu Evidenz - Die Vision von OHDSI  
Ines Reinecke, ines.reinecke@ukdd.de

## OHDSI community calls - weekly

<https://www.ohdsi.org/community-calls/>  
Tuesday, 11am ET (16:00 CET)



## OHDSI 10th Birthday

## 28 Days, 28 Phenotypes

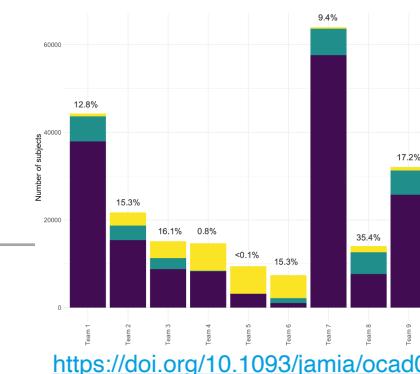


Join The Conversations!  
<https://www.ohdsi.org/phenotype-phebruary-2023/>

## OHDSI Titan Awards



## Study-a-thons Reproducibility Challenge, 2021



<https://doi.org/10.1093/jamia/ocad009>

# OHDSI Framework

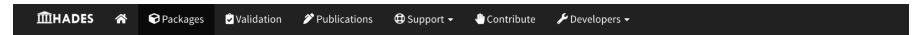


## DATA QUALITY ASSESSMENT

### SYNTHEA SYNTHETIC HEALTH DATABASE

Results generated at 2019-08-22 14:15:06 in 29 mins

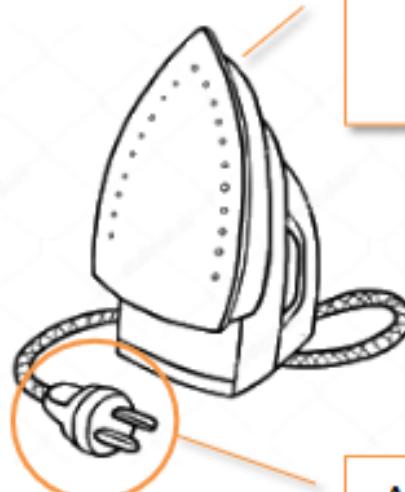
	Verification				Validation				Total			
	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass
Plausibility	159	21	180	88%	283	0	283	100%	442	21	463	95%
Conformance	637	34	671	95%	104	0	104	100%	741	34	775	96%
Completeness	369	17	386	96%	5	10	15	33%	374	27	401	93%
Total	1165	72	1237	94%	392	10	402	98%	1557	82	1639	95%



## Patient-level prediction

# OHDSI - OMOP CDM

"What's the adherence to my drug in the data assets I own?"



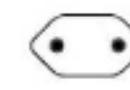
Analytical method:  
Adherence to Drug



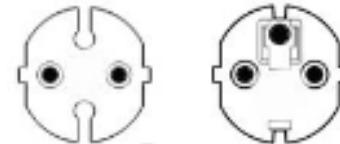
North America



Southeast Asia



China



Europe



UK



Japan



India



So Africa



Switzerland

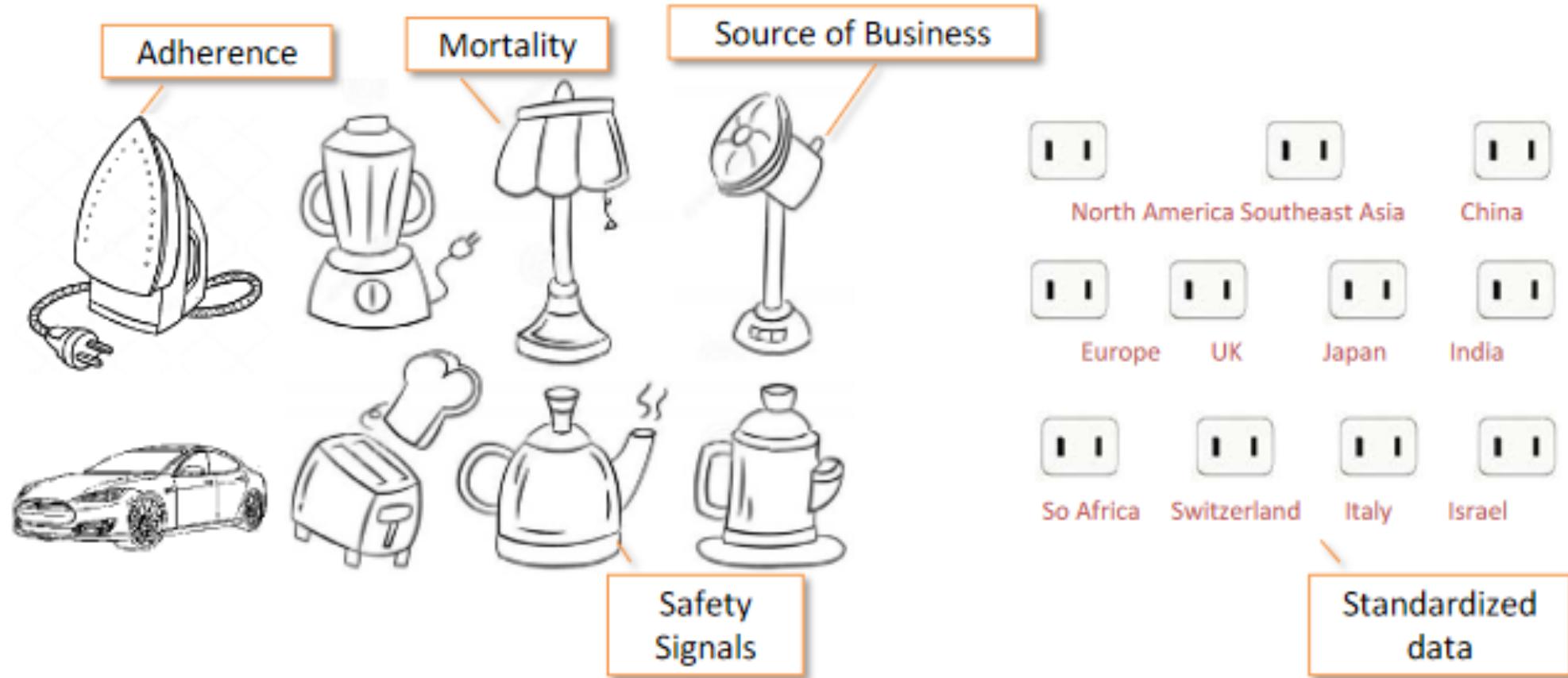


Italy

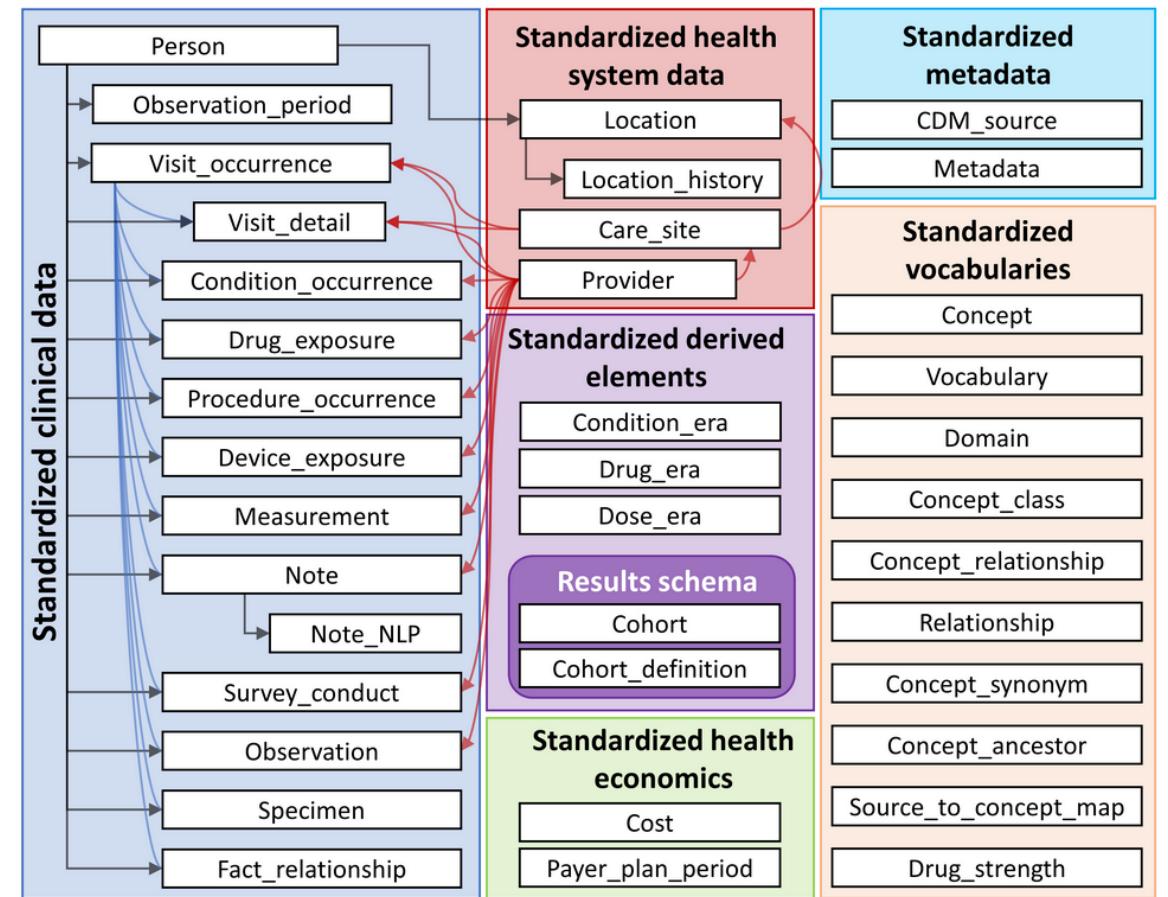


Israel

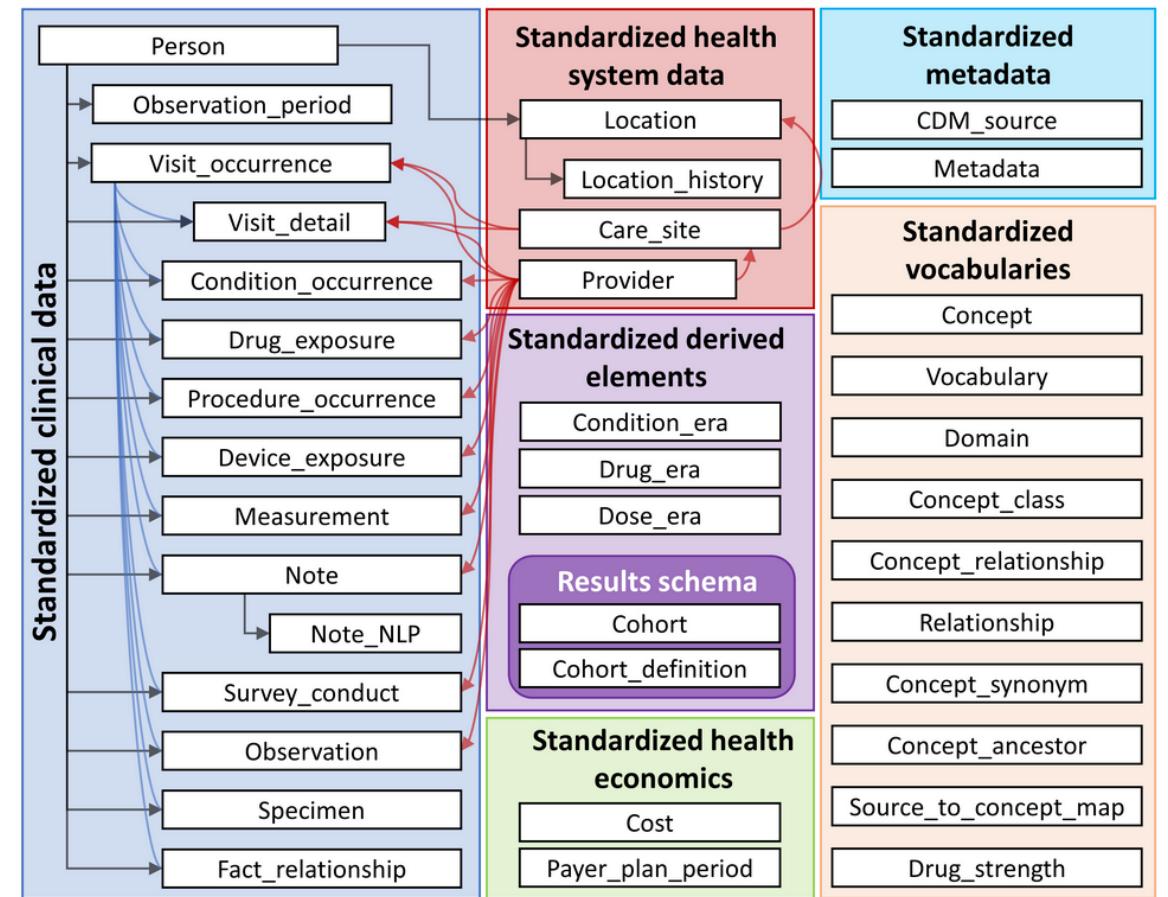
# OHDSI - OMOP CDM



# OHDSI - OMOP CDM



# OHDSI - OMOP CDM



# Sample Use Case

Lauren hat seit einigen Jahren starke Regelschmerzen, die in den letzten Jahren so schlimm geworden sind, dass Schmerzmedikamente kaum noch halfen. Erst nachdem eine Zyste in ihrem Eierstock geplatzt ist, wurde die Diagnose **Endometriose** gestellt.

Quellen:

- <https://www.endometriosis-uk.org/laurens-story> und
- <https://ohdsi.github.io/TheBookOfOhdsi/CommonDataModel.html>

# What we know about Lauren

Table PERSON (excerpt)		
attribute	content human readable/explaination	in database
PERSON_ID		1
GENDER_CONCEPT_ID	Female / weiblich	8532
YEAR_OF_BIRTH	1987	1987
MONTH_OF_BIRTH	3	3
DAY_OF_BIRTH	12	12
BIRTH_DATETIME	12.03.1987, 0:00:00 Uhr	1987-03-12 00:00:00
RACE_CONCEPT_ID	No matching concept	0
ETHNICITY_CONCEPT_ID	No matching concept	0

Age = 36 years

Birth date = March 3rd 1987

# Clinical Finding endometriosis - in OMOP CDM

Table CONDITION\_OCCURENCE (excerpt)

attribute	content human readable/explaination	in database
CONDITION_OCCURENCE_ID		964
PERSON_ID	reference to patient table	1
CONDITION_SOURCE_VALUE	Endometriose, nicht näher bezeichnet	N80.9
CONDITION_SOURCE_CONCEPT_ID	Endometriosis, unspecified	37091427

Endometriosis (ICD 10 GM Code N80.9) with concept ID 37091427 in OMOP

# Clinical Finding endometriosis - in OMOP CDM

Table CONDITION\_OCCURENCE (excerpt)

attribute	content human readable/explaination	in database
CONDITION_OCCURENCE_ID		964
PERSON_ID	reference to patient table	1
CONDITION_SOURCE_VALUE	Endometriose, nicht näher bezeichnet	N80.9
CONDITION_SOURCE_CONCEPT_ID	Endometriosis, unspecified	37091427
CONDITION_CONCEPT_ID	Endometriosis (disorder) in SNOMED (129103003)	433527

Endometriosis (ICD 10 GM Code N80.9) with concept ID 37091427 in OMOP

and mapping to standard concept 129103003 in SNOMED CT (OMOP concept ID 433527)

# Clinical Finding endometriosis - in OMOP CDM

Table CONDITION\_OCCURENCE (excerpt)

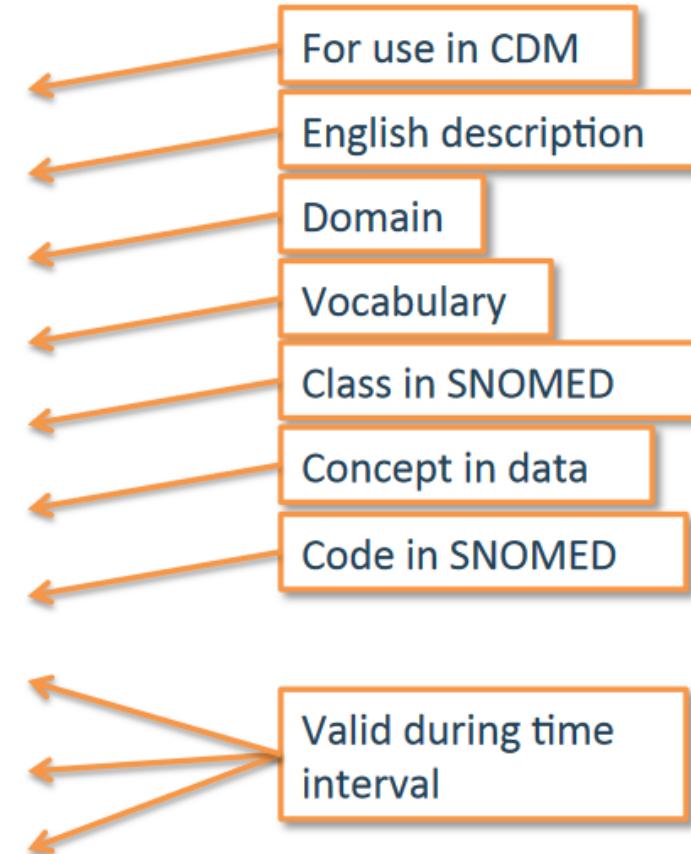
attribute	content human readable/explaination	in database
CONDITION_OCCURENCE_ID		964
PERSON_ID	reference to patient table	1
CONDITION_SOURCE_VALUE	Endometriose, nicht näher bezeichnet	N80.9
CONDITION_SOURCE_CONCEPT_ID	Endometriosis, unspecified	37091427
CONDITION_CONCEPT_ID	Endometriosis (disorder) in SNOMED (129103003)	433527

Endometriosis (ICD 10 GM Code N80.9) with concept ID 37091427 in OMOP

and mapping to standard concept 129103003 in SNOMED CT (OMOP concept ID 433527)

# OMOP Standard concepts...

CONCEPT_ID	313217
CONCEPT_NAME	Atrial fibrillation
DOMAIN_ID	Condition
VOCABULARY_ID	SNOMED
CONCEPT_CLASS_ID	Clinical Finding
STANDARD_CONCEPT	S
CONCEPT_CODE	49436004
VALID_START_DATE	01-Jan-1970
VALID_END_DATE	31-Dec-2099
INVALID_REASON	



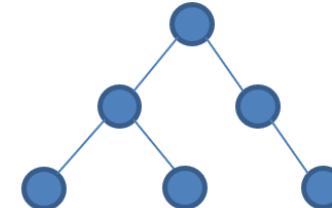
# ... and its relationships



All content: concepts in  
**concept**



Direct relationships between  
concepts in  
**concept\_relationship**



Multi-step hierarchical  
relationships pre-processed  
into  
**concept\_ancestor**