Implementation of OMOP and ConcePTION Common Data Models in CPRD GOLD: Risk of Bleeding and Cardiovascular Outcomes From Anticoagulant Use

Nicholas B. Hunt[1], Patrick Souverein[1], Marloes Bazelier[1], Nicola Barclay[2], Antonella Delmestri[2], Miriam Sturkenboom[3], Daniel Prieto-Alhambra[2], Helga Gardarsdottir[1,4,5] and Olaf Klungel[1,*]

The impact of the choice of common data model (CDM) approach on the study results in a real-world evidence (RWE) study is unknown. We aimed to determine potential differences in the results of an RWE study when data were mapped to two different CDMs, ConcePTION and OMOP. With the same instance of CPRD GOLD, data were mapped to both CDMs. Using the same programming steps, we estimated the risk of direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) on bleeding and cardiovascular (CVD) outcomes in patients with non-valvular atrial fibrillation. Baseline characteristics, incidence rates, and Cox proportional hazards ratios were compared between the analyses. OMOP and ConcePTION mapped study populations included 80,701 (93,350 person-years) and 76,726 exposed persons (100,135 person-years), respectively. DOACs showed no differential risk of CVD compared to VKAs in ConcePTION mapped data (HR 0.99, 95% CI [0.91; 1.08]), but protective effects in OMOP (HR 0.82, 95% CI [0.74; 0.90]). DOACs had a similar increase in risk of stroke (ConcePTION HR 1.19, 95% CI [1.02; 1.37]; OMOP HR 1.10, 95% CI [0.96; 1.26]). No increased risk of major bleeding was identified (ConcePTION HR 0.97, 95% CI [0.84; 1.13]; OMOP HR 0.90, 95% CI [0.78; 1.04]). OMOP gave lower effect estimates for CVD and equivalent risks of stroke and bleeding associated with DOACs use. This study highlights the challenges in repeating the same analysis across the two data CDMs. Differences potentially stem from the cohort construction, the identification of phenotypes in the different CDMs, and the use of imputed variables defined during mapping processes, such as drug exposure duration.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The employment of common data models (CDMs) to harmonize electronic healthcare data across multiple data sources can have an impact on study results. There is an obligation to better understand how these strategies could affect real-world evidence studies as they are employed throughout Europe and beyond.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ How do patient characteristics, outcome incidence rates, and effect estimates of a pharmacoepidemiologic case study differ when mapping real-world data to the general ConcePTION CDM, without semantic harmonization, compared to a general CDM (Observational Medical Outcomes Partnership [OMOP] CDM) that is independent of study questions and semantically mapped to common vocabularies?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ When the same electronic healthcare data are mapped to two different CDMs that differ in harmonization approaches and despite using the same protocol, there can be differences in the results of a pharmacoepidemiologic case study including study population size, baseline characteristics, and small differences in effect estimates.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study highlights the difficulties in repeating analyses using two different common data models. Researchers should be aware of explicit and implicit choices that are made when using a specific CDM, since it can impact the study output due to differences in phenotyping, data curation, or analytical technique being applied.

Received July 19, 2025; accepted February 10, 2026. doi:10.1002/cpt.70242

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK; [3]Department of Data Science & Biostatistics, Julius Global Health, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht, The Netherlands; [5]Department of Pharmaceutical Sciences, School of Health Sciences, University of Iceland, Reykjavik, Iceland. *Correspondence: Olaf Klungel (o.h.klungel@uu.nl)

Presentation: Oral presentation on August 27, 2024, at the International Society for Pharmacoepidemiology Annual Meeting in Berlin, Germany.

The use of multiple health databases in pharmacoepidemiologic studies can facilitate more robust assessments of drug safety and effectiveness.[1] Regulatory bodies such as the European Medicines Agency (EMA) mandate for the access and generation of real-world evidence (RWE) from multiple sources. This is necessary for comparing the safety and effectiveness of drugs across diverse countries and regions, while also considering variations in study populations and healthcare systems.[2,3] The heightened intricacies resulting from inter-database heterogeneity stem from variations in the recording, methods and purposes of information collection, alongside practical challenges like standardizing analyses across a distributed database network.[1,4,5]

Common data models (CDMs) are a methodology where data from a local data source are modeled to a standardized data structure and schema (syntactic harmonization). CDMs can facilitate standardized and federated analyses, while not overstepping ethical and legal constraints associated with multi-database studies.[6] CDMs offer efficiency to the investigator and by extension the regulatory agencies, through the use of standardized data and analytical programming; much is predefined prior to the conception of a specific protocol. Drug regulatory agencies started to use these methods after the Rofecoxib saga.[7] Regulatory agencies then established networks such as the FDA Sentinel System, and in Canada, the CNODES system.[8,9]

In Europe, the EMA created the European Network of Centers of Excellence in Pharmacoepidemiology & Pharmacovigilance (ENCePP). Multi-database studies using CDMs started from 2008 with EU-ADR, followed by many EMA-sponsored projects; throughout these projects, the use of CDMs evolved.[6,10,11] European projects that involved the use of a CDM were conducted under the umbrella of the EU Pharmacoepidemiology & Pharmacovigilance Research Network (EU PE&PV), IMI-ConcePTION and the Vaccine Monitoring Collaboration for Europe (VAC4EU) networks using the ConcePTION CDM, the IMI-European Health Data and Evidence Network (EHDEN), using the OMOP CDM, among others.[12–20] European harmonization of data structures with a CDM is supported by the EMA to sustainably increase the speed of pan-European pharmacoepidemiologic research output.[3] In 2022, the Data Analysis and Real-World Interrogation Network (DARWIN EU®) was set up by the EMA for rapid generation of evidence, using the OMOP CDM.[8,21–24]

Different strategies for multi-database studies and levels of harmonization may impact the results such as incomplete mappings and content differences, perhaps leading to varying effect estimates between harmonization strategies.[25–28] At the moment, two different types of general-use CDMs commonly used in Europe are the OMOP and ConcePTION CDMs. The structure of clinical tables is similar for the OMOP and ConcePTION CDMs; the key difference is that the ConcePTION CDM only requires syntactic harmonization to be done by the data access provider, whereas the OMOP CDM requires both syntactic and semantic harmonization (mapping of original coding system to a standardized vocabulary).[13] In the ConcePTION pipeline, semantic mapping is conducted using concept sets with all different source terminologies as part of the analysis script. Frequently, data sources that are mapping their data to OMOP CDM do this for the whole dataset, independent of the studies they will participate in. For the ConcePTION CDM, data instances may comprise the whole data set, but study-specific filling of the CDM is also possible, where only data intended for the study is fitted into the CDM.

The objective of this study was to compare the impact of the use of the ConcePTION CDM vs. the use of the OMOP CDM on the descriptive statistics and effect estimates of a pharmacoepidemiologic RWE study. To illustrate this, we conducted a case study on the risk of major bleeding and cardiovascular disease outcomes associated with the use of direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) in patients with non-valvular atrial fibrillation (NVAF), adapted from an earlier drug safety investigation commissioned by the EMA.[29]

METHODS

We conducted a cohort study using electronic primary care data (see **Figure 1**). The study was conducted by using two harmonization approaches on the same data source: the use of a CDM filled with study-specific data (ConcePTION) and a study-agnostic CDM (OMOP) including semantic harmonization.

Setting

Data were obtained from Clinical Practice Research Datalink (CPRD) GOLD, which consists of electronic health records from primary care practices throughout the United Kingdom (CPRD protocol 23_003125, institutional review board approval dated 28 December 2023). The July 2022 data instance was used in this study for both approaches to ensure consistency: CPRD GOLD contained information on 3.1 million current patients from 399 currently contributing primary care practices.[30] In the source data, diagnoses, referral, procedures, immunizations and tests are classified by the Read version 2 coding system, while drug information is recorded with Gemscript codes. These source codes were mapped to different coding systems for the OMOP CDM and drug information only for the ConcePTION CDM.

ConcePTION CDM

Data for persons with an oral anticoagulant prescription (see DOAC and VKA code list in **Appendix S1**) in the study period underwent the extract, transform, load (ETL) process to the ConcePTION CDM v2.2.[6] The ETL program was designed and used previously and is updated for every new study.[31] The ConcePTION CDM requires syntactic harmonization, but it does not require upfront semantic harmonization of clinical concepts to common vocabularies; the ConcePTION pipeline conducts semantic harmonization as part of the study analytical script. As such, it does not have a standard clinical

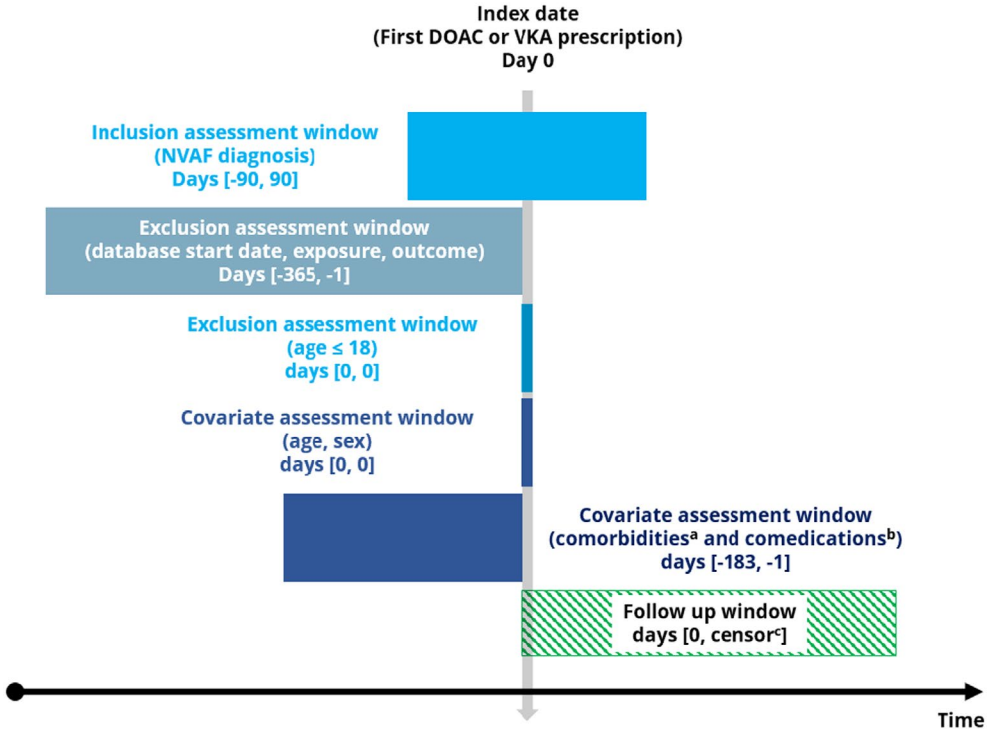

Figure 1 A graphical depiction of the study design. (**a**) Comorbidities: pulmonary embolism, deep vein thrombosis, hypertension, diabetes mellitus, liver disease, cancer, alcohol abuse, thrombocytopenia, gastrointestinal ulcer, cardiovascular disease, anemia, chronic lung disease, peripheral artery disease, angina, drug abuse, human immunodeficiency virus, and hypercholesterolemia. (**b**) Concomitant medication: angiotensin II antagonists, antidiabetics, antiplatelets, beta-blockers, calcium channel blockers, corticosteroids, diuretics, doxazosin, moxonidin, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, angiotensin-converting-enzyme inhibitors, aldosterone antagonists and direct vasodilators. (**c**) Outcome, discontinuation of study drugs, switch to other medication class (DOAC/VKA), loss to follow-up, death, move or end of the study period. DOACs, direct oral anticoagulant; NVAF, non-valvular atrial fibrillation; VKAs, vitamin K antagonist.

vocabulary or coding terminology and the original data elements are maintained.[13] The ConcePTION CDM contains the WHO Anatomical Therapeutic Chemical (ATC) codes as a variable to record medicines, so all drug product codes present in CPRD GOLD (BNF codes) were mapped to ATC codes during the ETL process. For clinical events (conditions), the source vocabulary was used. With the data in the standardized schema, the variables and analytical data sets were created and subsequently analyzed using a program that recognizes the local vocabulary for conditions and ATC for drugs.

OMOP CDM

The entirety of CPRD GOLD underwent the ETL process and was mapped to the OMOP CDM (V5.3). OMOP CDM was developed by the public-private partnership OMOP project, and it is now administered by the Observational Health Data Sciences and Informatics (OHDSI) community. OMOP provides semantic and syntactic harmonization so that each element of the database is mapped to the OMOP standard vocabulary (e.g., SNOMED for clinical concepts and RxNorm for drug concepts) and is fitted to a standardized data schema.[32–34] The code lists constructed in source vocabularies were matched to the OMOP CDM by data contained in the condition_source_value and drug_source_value of the CONDITION_OCCURANCE and DRUG_EXPOSURE tables, respectively (**Appendices S1 and S2**, original outcome and drug codes adapted from Souverein *et al.*).[29] The cohort, variables and analytical dataset were created and analyzed using software partly developed for the DARWIN EU® initiative. These included *Capr* to construct the concept sets of the drugs and conditions as well as cohort definitions, *CDMConnector* to reference to the CDM and to create the cohorts and *PatientProfiles* to identify the characteristics of the patients of the cohorts.[35–38]

Study population

The study population included people who initiated DOACs or VKAs (index date, drug code list in **Appendix S1**) with no prescription ≤365 days prior. At index date, patients must have had an NVAF diagnosis within ±90 days, have been aged ≥ 18, and have been registered at the GP practice for at least 365 days. Patients were followed up until the occurrence of the study outcome, a switch in medication to the other exposure class, the end of the last sequential prescription, the patient exiting the practice (death or transferring out), the last data delivery of the practice, or the end of the study period, whichever came first. Patients were excluded from the analysis if the outcome event had already occurred in the 365 days prior to the index date.

Exposure definition

CPRD GOLD does not contain the end date of use for each prescription, but provides several pieces of information that allow for its calculation. In the ConcePTION CPRD GOLD data, the end date of each DOAC prescription was estimated using an algorithm which accounts for the CPRD GOLD variables: *total quantity* (*qty*, number entered by the GP), *number of packs* (if *qty* is assumed to represent number of tablets) and *number of days*.[39] If missing or in case of estimating VKA prescription length, the median distance between ≥ 3 subsequent prescriptions for that specific medication (prodcode) was imputed per person, up to a maximum of 100 days.[29] Otherwise, an end date 28 days after the prescription date was imputed. In OMOP CPRD GOLD data, the field *drug_exposure_end_date* was estimated during the ETL process using an algorithm based on the prescribed *number of days* or, if missing, on the most frequent daily dose present for that specific medication (prodcode) in CPRD GOLD. If no match was found, then the *number of days* was set to 1.[26,40]

In ConcePTION modeled CPRD GOLD data, episodes of subsequent treatment were constructed independent of possible dose changes within a period. The treatment periods of DOACs or VKAs were made to allow a 30-day gap between the theoretical end date of one prescription and the start date of the next prescription, using AdhereR.[41,42] In OMOP CDM Standard Drug Eras were estimated from a combination of drug concepts mapped to the active ingredient present in the DRUG_EXPOSURE table with ≤ 30 days between them. For simplicity and consistency between the harmonization strategies, we did not consider overlapping prescriptions—that is, no exposure days were added at the end.

Outcome definition

We assessed three clinical outcomes and one negative control outcome (conditions code lists in **Appendix S2**): major bleeding (intracranial bleeding, gastrointestinal bleeding and other unclassified extracranial bleeding events),[43] all strokes (hemorrhagic and ischemic strokes), cardiovascular disease (including congestive heart failure, angina, myocardial infarction, coronary artery disease, aortic plaque and peripheral artery disease) and hip fractures (negative control outcome). The code lists for the clinical outcomes were based on earlier studies conducted on the topic including Souverein *et al*.[29] At the time these code lists were compiled and verified by a coding team including clinicians.

Confounding factors

Sex and age (continuous) were measured at index date. Concomitant medications measured ≤ 183 days prior to index date included non-steroidal anti-inflammatory drugs (NSAIDs), antidiabetics, diuretics, direct vasodilators, beta-blockers, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II antagonists, corticosteroids, selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), statins, alpha adrenergic blockers, aldosterone antagonists, doxazosin, moxonidin and antiplatelets (drug code list in **Appendix S1**). Comorbidities measured ≤ 183 days prior to index date included stroke, major bleeding, gastrointestinal ulcer, pulmonary embolism and deep vein thrombosis, thrombocytopenia, hypertension, cancer, diabetes mellitus, hypercholesterolemia, all cardiovascular disease, angina, peripheral artery disease, heart failure, anemia, chronic lung disease, liver disease and renal failure (condition code lists in **Appendix S2**).

Data analysis

Baseline characteristics were stratified by treatment group at baseline; means, standard deviations (SD), absolute totals and percentages were calculated. Incidence rates (IRs) for the measured outcomes expressed per 1000 person-years were calculated. We carried out a complete case analysis to handle potential missing data. In both strategies, the same data analysis code was used to calculate these metrics.

Inferential analyses

Cox proportional hazards regression models were used to calculate the relative risk of the outcomes of interest (stroke, major bleeding, cardiovascular disease) in DOAC users compared to VKA users, expressed as a hazard ratio (HR) and 95% confidence intervals (CI). To account for measured confounding, the model was adjusted using the measured covariates considered to be confounders, while the association between DOAC vs. VKA use and the negative control outcome (hip fracture) indicated the presence of unmeasured confounding.

Measures of comparison

Differences between the CDMs were shown through potential variations in the effect estimates (HRs), counts of the outcomes (number of events), incidence rates of outcome events, and descriptive statistics of the baseline characteristics. The estimate agreement was assessed by the overlapping 95% confidence intervals of the HRs and IRs.

The measure of differences in the effect estimates (HRs) and confidence intervals between the two CDM strategies was assessed through the calculation of standardized differences and the corresponding 95% CIs, as adapted from Franklin *et al*.[44]:

$$z = \frac{\hat{\theta}_{\mathrm{CDM}} - \hat{\theta}_{\mathrm{CP}}}{\sqrt{\hat{\sigma}^2_{\mathrm{CDM}} + \hat{\sigma}^2_{\mathrm{CP}}}}$$

The $\hat{\theta}^2$ is the log hazard ratio and the $\hat{\sigma}^2$ is the variance for each estimate. If we take 95% confidence intervals, then $\alpha = 0.05$, and $|z| > 1.96$, then we would reject the null hypothesis that there are no significant differences between harmonization strategies.[44]

RESULTS

After application of the eligibility criteria, the study population included 80,701 persons (43.7% DOAC users) in the OMOP CDM and 76,726 persons (43.5% DOAC users) in the ConcePTION CDM (**Table 1**). The study population in ConcePTION CPRD and OMOP CPRD data had a similar age at index date (mean difference 0.5 years greater in ConcePTION) and a similar sex balance (mean difference 0.3% greater in ConcePTION).

The proportion of patients with any of the comorbidities recorded 183 days prior to index date in the ConcePTION CPRD data was similar to the OMOP CPRD data for stroke (mean percentage difference + 0.7), CVD (diff +0.5%), any neoplasm and cancer (diff +0.2%), heart failure (diff +0.8%), chronic lung disease (diff +0.5%), renal failure (diff +0.1%), anemia (diff +0.2%), angina (diff +0.1%), deep vein thrombosis and pulmonary embolism (diff −0.2%), hypertension (diff −0.4%) and diabetes (diff −0.1%). The number of patients identified as using concomitant medications was generally higher in ConcePTION vs. OMOP CPRD data, with exceptions: corticosteroids (diff −9.4%), NSAIDs (diff −6.6%) and aldosterone antagonists (diff −0.3%). ACE-inhibitors (diff +5.3%), β-blockers (diff +6.7%), calcium channel blockers (diff +5.3%), diuretics (diff +5.3%), PPIs (diff +5.7%) and statins (diff +8.1%) all were > 5% greater percentage difference in ConcePTION CPRD data than OMOP CPRD data.

The total follow-up time of the included patients was greater in all four outcome cohorts in ConcePTION CPRD data than in OMOP CPRD data (**Figure 2**). For example, the major bleeding cohort contained a total of 100,135 person-years in the ConcePTION CPRD data and 93,350 person-years in the OMOP CPRD data. This difference seems to have been driven predominantly by a greater total follow-up time in VKA users (56,407 person-years in ConcePTION vs. 49,915 person-years in OMOP). This trend was consistent in the stroke, CVD, and hip fracture cohorts (**Figure 2**).

The incidence rates of major bleeding (IR ConcePTION 7.6, 95% CI [7.1; 8.2]; OMOP 8.1 [7.6; 8.7]) and hip fracture (4.1 [3.7; 4.5]; 4.7 [4.2; 5.1]) were similar between ConcePTION and OMOP CPRD data. The incidence rate of CVD events differed, with a higher total IR in ConcePTION CPRD data (IR 23.0, 95% CI [22.0; 24.0]) than in OMOP CPRD data (18.1, [17.2; 19.0]). The IR of stroke (7.8, [7.2; 8.4]) was smaller in ConcePTION than in OMOP CPRD data (9.3, 95% CI [8.7; 10.0]). Stroke and hip fracture outcomes had a lower number of total outcome

Table 1 Baseline characteristics of the cohort study in CPRD GOLD (United Kingdom) mapped to the ConcePTION CDM and to the OMOP CDM

	ConcePTION CDM		OMOP CDM		Difference ConcePTION to OMOP (%)	
	DOAC	VKA	DOAC	VKA	DOAC	VKA
Study population size, *n*	33,379	43,347	35,267	45,434	–	–
Male (%)	18,532 (55.5)	24,201 (55.8)	19,511 (55.3)	25,181 (55.4)	0.2	0.4
Age at index date (mean (SD))	75.03 (10.80)	74.20 (10.20)	74.57 (11.00)	73.75 (10.39)	–	–
Comorbidities						
Anemia (%)	439 (1.3)	569 (1.3)	396 (1.1)	494 (1.1)	0.2	0.2
Angina (%)	257 (0.8)	358 (0.8)	249 (0.7)	338 (0.7)	0.1	0.1
Any neoplasm or cancer (%)	947 (2.8)	1074 (2.5)	941 (2.7)	1027 (2.3)	0.1	0.2
Cardiovascular disease (%)	1438 (4.3)	2221 (5.1)	1367 (3.9)	2055 (4.5)	0.4	0.6
Chronic lung disease (%)	1093 (3.3)	1464 (3.4)	996 (2.8)	1276 (2.8)	0.5	0.6
Diabetes (%)	439 (1.3)	684 (1.6)	484 (1.4)	753 (1.7)	−0.1	−0.1
Deep vein thrombosis or pulmonary embolism (%)	310 (0.9)	617 (1.4)	390 (1.1)	740 (1.6)	−0.2	−0.2
Gastrointestinal ulcer (%)	39 (0.1)	75 (0.2)	37 (0.1)	68 (0.1)	0.0	0.1
Heart failure (%)	2127 (6.4)	3182 (7.3)	1999 (5.7)	2953 (6.5)	0.7	0.8
Hypercholesterolemia (%)	<5 (0.0)	13 (0.0)	78 (0.2)	145 (0.3)	−0.2	−0.3
Hypertension (%)	724 (2.2)	991 (2.3)	858 (2.4)	1293 (2.8)	−0.2	−0.5
Liver disease (%)	64 (0.2)	59 (0.1)	58 (0.2)	54 (0.1)	0.0	0.0
Major bleeding (%)	117 (0.4)	139 (0.3)	108 (0.3)	126 (0.3)	0.1	0.0
Peripheral artery disease (%)	104 (0.3)	165 (0.4)	128 (0.4)	185 (0.4)	−0.1	0.0
Renal failure (%)	451 (1.4)	1020 (2.4)	445 (1.3)	989 (2.2)	0.1	0.2
Stroke (%)	1785 (5.3)	2196 (5.1)	1593 (4.5)	2036 (4.5)	0.8	0.6
Thrombocytopenia (%)	13 (0.0)	27 (0.1)	9 (0.0)	18 (0.0)	0.0	0.1
Concomitant medications						
Angiotensin-converting-enzyme inhibitors (%)	10,749 (32.2)	16,346 (37.7)	9784 (27.7)	14,418 (31.7)	4.5	6.0
Aldosterone antagonists (%)	1126 (3.4)	1713 (4.0)	1235 (3.5)	1952 (4.3)	−0.1	−0.3
Alpha adrenergic blockers (%)	2393 (7.2)	3717 (8.6)	2172 (6.2)	3324 (7.3)	1.0	1.3
Angiotensin II antagonists (%)	5064 (15.2)	7004 (16.2)	4752 (13.5)	6307 (13.9)	1.7	2.3
Antidiabetic drugs (%)	4616 (13.8)	6063 (14.0)	4143 (11.7)	5289 (11.6)	2.1	2.4
Beta blocking agents (%)	14,208 (42.6)	22,416 (51.7)	13,289 (37.7)	19,832 (43.7)	4.9	8.0
Calcium channel blockers (%)	11,258 (33.7)	15,666 (36.1)	10,126 (28.7)	13,954 (30.7)	5.0	5.4
Corticosteroids (%)	4113 (12.3)	5122 (11.8)	7773 (22.0)	9495 (20.9)	−9.7	−9.1
Direct vasodilators (%)	65 (0.2)	111 (0.3)	5 (0.0)	17 (0.0)	0.2	0.3
Diuretics (%)	11,544 (34.6)	18,515 (42.7)	10,678 (30.3)	16,735 (36.8)	4.3	5.9

(Continued)

Table 1 (Continued)

	ConcePTION CDM		OMOP CDM		Difference ConcePTION to OMOP (%)	
	DOAC	VKA	DOAC	VKA	DOAC	VKA
Doxazosin (%)	2367 (7.1)	3630 (8.4)	2147 (6.1)	3246 (7.1)	1.0	1.3
Moxonidin (%)	148 (0.4)	290 (0.7)	125 (0.4)	261 (0.6)	0.0	0.1
Non-steroidal anti-inflammatories (%)	3113 (9.3)	4792 (11.1)	6019 (17.1)	7598 (16.7)	−7.8	−5.6
Proton pump inhibitors (%)	13,339 (40.0)	16,380 (37.8)	12,254 (34.7)	14,436 (31.8)	5.3	6.0
Statins (%)	16,704 (50.0)	22,539 (52.0)	15,094 (42.8)	19,683 (43.3)	7.2	8.7
Selective serotonin reuptake inhibitors (%)	2821 (8.5)	3143 (7.3)	2598 (7.4)	2778 (6.1)	1.1	1.1

Comorbidities and concomitant medications measured within 183 days preceding the index date.
CDM, common data model; DOACs, direct oral anticoagulants; SD, standard deviation; VKAs, vitamin K antagonists.

events in ConcePTION compared to OMOP CPRD data (729 in ConcePTION vs. 814 in OMOP and 413 vs. 436, despite a longer total follow-up time).

In the Cox proportional hazards models (**Figure 3**), all outcomes had a numerically lower HR point estimate in OMOP CPRD data than in ConcePTION CPRD data. Most significantly, DOACs showed no increased risk of CVD events compared to VKAs in ConcePTION CPRD data (adjusted HR 0.99, 95% CI [0.91; 1.08]), but protective effects in OMOP CPRD data (adjusted HR 0.82, 95% CI [0.74; 0.90]). In ConcePTION CPRD data, DOACs slightly increased the risk of stroke compared to VKAs (adjusted HR 1.19, 95% CI [1.02; 1.37]) and (not statistically significant) in OMOP CPRD data (adjusted HR 1.10, 95% CI [0.96; 1.26]). Conversely, there was no increased risk of major bleeding for DOACs in both ConcePTION (adjusted HR 0.98, 95% CI [0.85; 1.13]) and OMOP CPRD data (adjusted HR 0.90, 95% CI [0.78; 1.04]). We observed an unexpected association between DOAC users and a higher risk of hip fracture (negative control outcome) in both analyses, with HR point estimates numerically higher in ConcePTION (HR 1.80, 95% CI [1.48; 2.19]) vs. OMOP CPRD data (HR 1.32, 95% CI [1.08; 1.61]). All 95% CIs of the Cox models overlap except for CVD adjusted, representing agreement for all effect estimates except CVD (**Figure 3**). In all cases we rejected the null hypothesis that there are no differences because the standardized differences for major bleeding ($z = 11.1$), stroke ($z = 10.0$), CVD ($z = 57.0$) and hip fracture ($z = 60.0$) were all greater than 1.96.

DISCUSSION

Several differences were found for study results when CPRD GOLD was mapped to the OMOP CDM compared to when it was mapped to the ConcePTION CDM. In OMOP CPRD, DOAC users had a lower risk of CVD events compared to VKA users (HR 0.82, 95% CI [0.74; 0.90]), an association that was not seen in ConcePTION CPRD data (HR 0.99, 95% CI [0.91; 1.08]). However, DOAC users had a similar risk of stroke in both the ConcePTION (HR 1.19, 95% CI [1.02; 1.37]) and OMOP approach (HR 1.10, 95% CI [0.96; 1.26]). The negative control outcome (hip fracture) departed more from the null in ConcePTION (HR 1.80, 95% CI [1.48; 2.19]) than in OMOP CPRD data (HR 1.32, 95% CI [1.08; 1.61]), suggesting residual confounding remained stronger in the former vs. the latter. In general, the procedure implemented in OMOP CPRD data led to numerically lower effect estimates (hazard ratios), higher incidence of outcomes (except CVD), and a lower number of co-medications recorded (except most notably, corticosteroids and NSAIDs).

Taking corticosteroids as an example: we saw a 9.4% difference in its use between ConcePTION and OMOP CPRD data. We selected drugs classified in the hierarchy ATC class H02 for ConcePTION CPRD data, as usual practice for someone working in the confines of this drug ontology. We classified it differently in OMOP by including all the active substances (ingredients, defined by RxNorm codes) contained within this ATC class, which in turn may extend to other ATC classes (such as topical products). However, most of the risk estimates had overlapping confidence

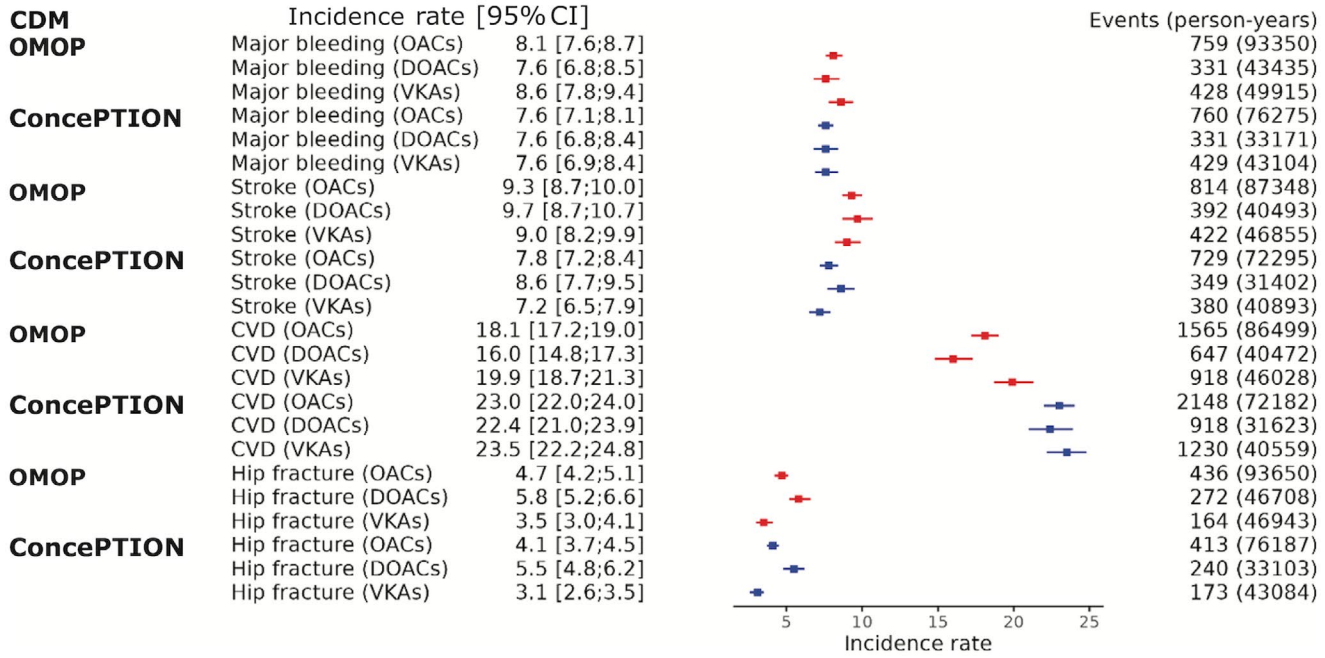

Figure 2 Incidence rate and number of events for major bleeding, stroke, cardiovascular disease and hip fracture (negative outcome) in CPRD GOLD using the ConcePTION CDM or the OMOP CDM. 95% CI, 95% confidence interval; CDM, common data model; CVD, Cardiovascular disease; DOACs, direct oral anticoagulants; OACs, oral anticoagulants; VKAs, vitamin k antagonists.

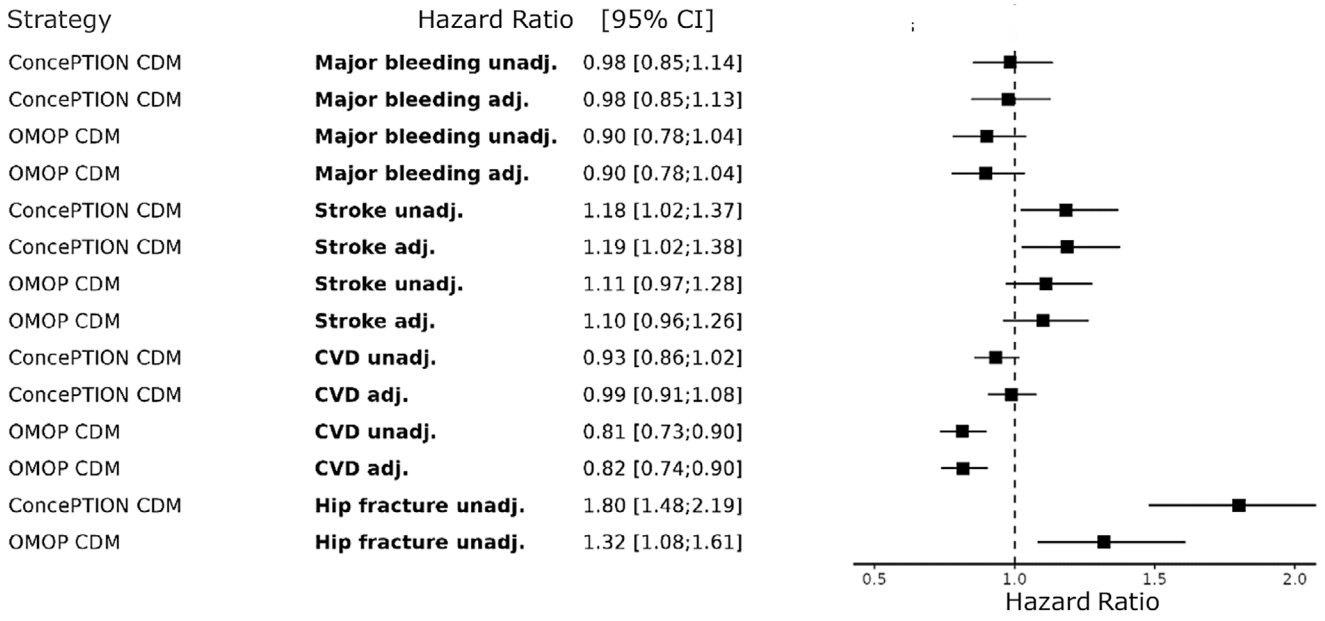

Figure 3 Cox proportional hazards regression of direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) for the risk of major bleeding, any stroke, any cardiovascular disease (CVD) event, and hip fractures (negative outcome) in CPRD GOLD mapped to the ConcePTION CDM and the OMOP CDM. 95% CI, 95% confidence interval; CDM, common data model; CVD, cardiovascular disease; DOACs, direct oral anticoagulants; OACs, oral anticoagulants; VKAs, vitamin K antagonists.

intervals; the metric prespecified at protocol stage to detect relevant differences.

The design differences in the CDM reflect the semantic methods employed on the data. OMOP CDM was developed with an emphasis on study conduct efficiency through the complex *a priori* process of (semantic) mapping to standard concepts. Whereas ConcePTION CDM was developed to maintain the heterogeneity inherent in European health data, while at the same time being faster and more flexible to employ due to the lack of upfront semantic harmonization.[13] Syntactic harmonization through a CDM filled with study-specific data in essence reorganizes the data schema and variable names for only a selection of data. In both

CDMs this is prespecified but in a CDM filled with study-specific data, like ConcePTION CDM, the ETL programme was executed at the time of the study.

We found that despite a lower study population size in ConcePTION CPRD data (e.g. the bleeding cohort consisted of 76,726 vs. 80,701 persons in OMOP), the follow-up time was greater (100,135 vs. 93,350 person-years in OMOP). This was largely driven by a higher estimation of treatment duration of VKAs in ConcePTION (56,407 vs. 49,915 person-years in OMOP), something that is user-defined during the ETL process and programmed in study variable creation steps. The estimation of the prescription duration of VKAs is more challenging than for DOACs, due to the treatment course being dependent on regular INR measurements. There is a source of variation due to the differences in how treatment duration was defined for each instance of data in the CDM. Sources of the potential difference in the study population size are the definition of the NVAF phenotype and OAC drug concepts and their subsequent identification in the data, as well as the prior data availability per patient. In the scope of cohort construction, the DOAC and VKA drug concepts are comparatively straightforward, defined by the ingredient concept IDs: the balance of the DOAC to VKA users differs by only 0.2%. Although the ingredient concept ID was used for the OMOP analysis, OACs are not used as a stand-alone combination product from different ATC classes. The identification of the NVAF phenotype remains less clear, and an analysis on the quantification of the events of each component of the eligibility criteria would be beneficial. Other origins of these cohort size differences could be due to the cohort construction method used for each of the analyses, as well as the implementation of each CDM and its mapping.

Compared to other CDMs including PCORnet, Mini-Sentinel CDM and CSISC SDTM, OMOP CDM has greater data elements and broader terminology for how it can be applied to different research questions.[45] The early iterations of mapping CPRD GOLD to the OMOP CDM proved acceptable mapping and completeness, which only improved through continuous iterations.[26] In earlier iterations of US data mapped to the OMOP CDM, differences between the effect estimates of six drug-outcome pairs generated from data mapped to the OMOP CDM and the Mini-Sentinel CDM have been previously identified. However, these were thought to be a result of choices in the analytic approach.[25] Similarly, in this study, despite a single protocol for the studies in the two CDMs, the output could have differed due to these small differences in analytics and the results here must be considered with this in mind. More generally, CDMs that use semantic mapping, like OMOP CDM, provide a greater degree of standardization and therefore interoperability but are inherently more likely to be susceptible to data quality issues than CDMs that do not map to a standard vocabulary.

Both OMOP and ConcePTION CDMs have their strengths and limitations. The OMOP CDM is longer established and as such, it involves not only data standardization but also structural and analytic programming developed to specifically work within its confines. Both CDMs are in their relative infancy of use in Europe, and the projects for which they are being used will increase their output in the coming years. The same methods applied to all electronic healthcare data in a federated analysis may reduce the flexibility of the analysis. Local expertise based on knowledge of the healthcare system and data contained may influence analytic strategy. Particularly, in the case of specific phenotypes or medicinal products and devices. It is important to understand the impact the cohort construction and analytic parameters can have when interpreting study output, as differences in implementation of the same study could occur due to those underlying mechanisms.

There were several limitations to the comparison between ConcePTION and OMOP CDMs. First, the same analytic program cannot be used in the two approaches. In using tools developed specifically for the OMOP CDM by the OHDSI community to standardize analytics for data mapped to a CDM, these cannot be used with ConcePTION CDM data or elsewhere.[46] Small syntax differences could potentially impact the results in a differential way, and any comparisons made should be made with caution. Second, the completeness of the mapping to a CDM may vary per database and data access provider. The use of one data source means that generalizing the results to all instances of data mapped to these CDMs may therefore be limited. Third, we were limited to one data source per approach and three determinant-outcome associations. Generalisability improvements could be achieved by analyzing a more extensive array of determinant-outcome associations in future studies. Fourth, clinical and drug code lists matching between the source codes to the OMOP *standard_concept_id* via the recorded source values in the CDM could lead to different classifications of the same drug product. For example, the drug ingredient *standard_concept_id* could account for drugs outside the ATC class, which specifies the drug concepts in ConcePTION. Finally, this study did not specifically compare each step of the algorithms applied within each CDM to better understand where potential syntactic differences arose, nor was an analysis of non-overlap between study populations done due to a lack of patient-level information in the analytic dataset.

Both ConcePTION and OMOP CDMs provide a level of standardization that allows for an efficient federated analysis of real-world data (RWD). There are, however, fundamental differences in their design, not limited to the addition of semantic harmonization employed by the latter. The OMOP CDM has an analytic approach that is streamlined and directed by accompanying standard analytical and data pre-processing packages. Users should pay attention to methodological choices that take place during mapping, the construction of analytical datasets, and data analytics. These are subject to standard pipelines that may not be suitable for the chosen research question and study design.

In our analysis, there were some small differences in the study output from data mapped to the ConcePTION and the OMOP CDMs. Output from the latter showed DOACs to have slightly numerically (but not significantly) lower effect estimates for most bleeding and cardiovascular outcome risks, compared to VKAs, than in the study output from ConcePTION CDM. Similar results were observed for the negative control outcome (hip fracture), which could be a useful metric to measure differences in analyses in detecting unmeasured confounding. In the context of these results, careful consideration of the outputs from the analysis

of different mapping CDMs should be made, particularly with regard to phenotyping and the use of imputed variables defined during mapping processes such as drug exposure duration. This variable is imputed using OMOP conventions on the estimation of the end date of drug exposure when it is missing, which is the case in many European electronic healthcare data sources.[47] Individual prescription duration is highly dependent on a multitude of factors including medicinal product, indication, and data sources. This is particularly poignant in the case of DOACs and VKAs, where the duration of the latter differs from patient to patient to a great extent. These reasons likely had an impact on the resulting incidence rates and effect estimates, and therefore, careful consideration should be given to the use of imputed or predefined variables in RWD, and in particular, causal inference studies.

Heterogeneity in effect estimates generated from the analysis of each CDM could lead to different decision-making in both the regulatory and clinical domains. The approach undertaken should account for not only each contributing database but also the harmonization that the underlying data has undergone, particularly with respect to phenotyping, syntactic, algorithmically defined variables, and the standardized analytic strategy used upon the mapped data. The scope of future research should focus on the implementation of study design and analytics in different environments since variations can affect the overall study output, while keeping in mind that validity should always outweigh efficiency.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

N.B.H. is employed within the DARWIN EU® project, but not at the time of the study. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

N.B.H. wrote the manuscript, N.B.H., P.S., M.B., H.G., M.S., D.P.-A., and O.K. designed the research; N.B.H. and N.B. performed the research, N.B.H., P.S., M.B., M.S., D.P.-A., H.G., and O.K. analyzed the data; P.S., M.S, A.D., and D.P.A. contributed analytical tools.

1. Platt, R.W. *et al*. How pharmacoepidemiology networks can manage distributed analyses to improve replicability and transparency and minimize bias. *Pharmacoepidemiol. Drug Saf.* **29**, 3–7 (2019).
2. Lai, E.C.-C., Stang, P., Yang, Y.-H.K., Kubota, K., Wong, I.C.K. & Setoguchi, S. International multi-database pharmacoepidemiology: potentials and pitfalls. *Curr. Epidemiol. Rep.* **2**, 229–238 (2015).
3. EMA. HMA-EMA Joint Big Data Taskforce-summary report Summary report (2019).
4. Toh, S. Analytic and data sharing options in real-world multidatabase studies of comparative effectiveness and safety of medical products. *Clin. Pharmacol. Ther.* **107**, 834–842 (2019).
5. Klungel, O.H. *et al*. Multi-centre, multi-database studies with common protocols: lessons learnt from the IMI PROTECT project. *Pharmacoepidemiol. Drug Saf.* **25**, 156–165 (2016).
6. Gini, R. *et al*. Different strategies to execute multi-database studies for medicines surveillance in real world setting: a reflection on the European model. *Clin. Pharmacol. Ther.* **108**, 228–235 (2020).
7. Jüni, P., Nartey, L., Reichenbach, S., Sterchi, R., Dieppe, P.A. & Egger, M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* **364**, 2021–2029 (2004).
8. Platt, R., Wilson, M., Chan, K.A., Benner, J.S., Marchibroda, J. & McClellan, M. The new Sentinel Network – improving the evidence of medical-product safety. *N. Engl. J. Med.* **361**, 645–647 (2009).
9. Suissa, S. *et al*. CNODES: the Canadian network for observational drug effect studies. *Open Med.* **6**, e134 (2012).
10. Kurz, X. & Perez-Gutthann, S. Strengthening standards, transparency, and collaboration to support medicine evaluation: ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). *Pharmacoepidemiol. Drug Saf.* **27**, 245–252 (2018).
11. Trifirò, G. *et al*. Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how? *J. Intern. Med.* **275**, 551–561 (2014).
12. van den Ham, H.A. *et al*. Major bleeding in users of direct oral anticoagulants in atrial fibrillation: a pooled analysis of results from multiple population-based cohort studies. *Pharmacoepidemiol. Drug Saf.* **30**, 1339 (2021).
13. Thurin, N.H. *et al*. From inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. *Clin. Pharmacol. Ther.* **111**, 321–331 (2022).
14. Sturkenboom, M. *et al*. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. *Vaccine* **38**, B1–B7 (2020).
15. Innovative Medicines Initiative. European Health Data and Evidence Network (EHDEN) <https://www.imi.europa.eu/projects-results/project-factsheets/ehden>.
16. Coloma, P.M. *et al*. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR project. *Pharmacoepidemiol. Drug Saf.* **20**, 1–11 (2011).
17. Valkhoff, V.E. *et al*. Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries in the SOS project: what size of data platforms and which study designs do we need to assess safety issues? *BMC Pediatr.* **13**, 192 (2013).
18. But, A. *et al*. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. *Diabetologia* **60**, 1691–1703 (2017).
19. Roberto, G. *et al*. Identifying cases of type 2 diabetes in heterogeneous data sources: strategy from the EMIF project. *PLoS One* **11**, 160648 (2016).
20. Trifirò, G. *et al*. Use of azithromycin and risk of ventricular arrhythmia. *CMAJ* **189**, E560–E568 (2017).
21. Platt, R. *et al*. The U.S. Food and Drug Administration's Mini-Sentinel Program: Status and direction. *Pharmacoepidemiol. Drug Saf.* **21**, 1–8 (2012).
22. Ball, R., Robb, M., Anderson, S.A. & Dal Pan, G. The FDA's sentinel initiative – a comprehensive approach to medical product surveillance. *Clin. Pharmacol. Ther.* **99**, 265–268 (2016).
23. HealthCanada. Canadian Network for Observational Drug Effects Studies (CNODES). https://www.cnodes.ca/.
24. Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency. https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu.
25. Xu, Y. *et al*. A comparative assessment of observational medical outcomes partnership and mini-sentinel common data models

and analytics: implications for active drug safety surveillance. *Drug Saf.* **38**, 749–765 (2015).
26. Matcho, A., Ryan, P., Fife, D. & Reich, C. Fidelity assessment of a clinical practice research datalink conversion to the OMOP common data model. *Drug Saf.* **37**, 945–959 (2014).
27. Zhou, X. *et al*. An evaluation of the THIN database in the OMOP common data model for active drug safety surveillance. *Drug Saf.* **36**, 119–134 (2013).
28. Schneeweiss, S., Brown, J.S., Bate, A., Trifirò, G. & Bartels, D.B. Choosing among common data models for real-world data analyses fit for making decisions about the effectiveness of medical products. *Clin. Pharmacol. Ther.* **107**, 827–833 (2020).
29. Souverein, P. *et al*. Comparing risk of major bleeding between users of different oral anticoagulants in patients with nonvalvular atrial fibrillation. *Br. J. Clin. Pharmacol.* **87**, 988–1000 (2020).
30. MHRA. Release Notes for CPRD GOLD July 2022 (2022) https://doi.org/10.48329/ty3h-h728.
31. Abtahi, S. *et al*. Impact of 2018 EU risk minimisation measures and revised pregnancy prevention programme on utilisation and prescribing trends of medicinal products containing valproate: an interrupted time series study. *Drug Saf.* **46**, 689 (2023).
32. Stang, P.E. *et al*. Advancing the science for active surveillance: rationale and design for the observational medical outcomes partnership. *Ann. Intern. Med.* **153**, 600–606 (2010).
33. Marc Overhage, J., Ryan, P.B., Reich, C.G., Hartzema, A.G. & Stang, P.E. Validation of a common data model for active safety surveillance research. *J. Am. Med. Inform. Assoc.* **19**, 54 (2012).
34. Hripcsak, G. *et al*. Observational Health Data Sciences and Informatics (OHDSI): opportunities for observational researchers. *Stud. Health Technol. Inform.* **216**, 574–578 (2015).
35. Black, A., Gorbachev, A., Burn, E. & Sabate, M.C. CDMConnector: Connect to an OMOP Common Data Model (2023).
36. Burn, E. CodelistGenerator: Generate Code Lists for the OMOP Common Data Model. R package version 2.0.0 (2023).
37. Lavallee, M. & Capr, B.A. Cohort Definition Application Programming (2023).
38. Sena, A., Gilbert, J., Rao, G., Cruz, F.A. & Schuemie, M. CohortGenerator: An R Package for Cohort Generation Against the OMOP CDM (2023).
39. Medicines & Healthcare products Regulatory Agency. CPRD GOLD Data Specification version 2.5 (2022).
40. Therapy | Janssen CDM Documentation <https://ohdsi.github.io/ETL-LambdaBuilder/CPRD/CPRD_Therapy_STEM.html>.
41. Gardarsdottir, H., Souverein, P.C., Egberts, T.C.G. & Heerdink, E.R. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J. Clin. Epidemiol.* **63**, 422–427 (2010).
42. Dima, A.L. & Dediu, D. Computation of adherence to medication and visualization of medication histories in R with AdhereR: towards transparent and reproducible use of electronic healthcare data. *PLoS One* **12**, e0174426 (2017).
43. Schulman, S. & Kearon, C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J. Thromb. Haemost.* **3**, 692–694 (2005).
44. Franklin, J.M. *et al*. Nonrandomized real-world evidence to support regulatory decision making: process for a randomized trial replication project. *Clin. Pharmacol. Ther.* **107**, 817–826 (2020).
45. Garza, M., Del Fiol, G., Tenenbaum, J., Walden, A. & Zozus, M.N. Evaluating common data models for use with a longitudinal community registry. *J. Biomed. Inform.* **64**, 333 (2016).
46. OHDSI. Health Analytics Data-to-Evidence Suite (HADES) <https://github.com/OHDSI/Hades> (2021).
47. OHDSI. OMOP CDM v5.4 Specification Documentation GitHub: OHDSI <https://ohdsi.github.io/CommonDataModel/cdm54.html#drug_exposure> (2025).