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ORIGINAL RESEARCH ARTICLE

A Comparative Assessment of Observational Medical Outcomes Partnership and Mini-Sentinel Common Data Models and Analytics: Implications for Active Drug Safety Surveillance

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Abstract

Introduction An often key component to coordinating surveillance activities across distributed networks is the design and implementation of a common data model (CDM). The purpose of this study was to evaluate two drug safety surveillance CDMs from an ecosystem perspective to better understand how differences in CDMs and analytic tools affect usability and interpretation of results.

Methods Humana claims data from 2007 to 2012 were mapped to Observational Medical Outcomes Partnership (OMOP) and Mini-Sentinel CDMs. Data were described and compared at the patient level by source code and mapped concepts. Study cohort construction and effect estimates were also compared using two different analytical methods—one based on a new user design implementing a high-dimensional propensity score (HDPS) algorithm and the other based on univariate self-controlled case series (SCCS) design—across six established positive drug-outcome pairs to learn how differences in CDMs and analytics influence steps in the database analytic process and results.

Results Claims data for approximately 7.7 million Humana health plan members were transformed into the two CDMs. Three health outcome cohorts and two drug cohorts showed differences in cohort size and constituency between Mini-Sentinel and OMOP CDMs, which was a result of multiple factors. Overall, the implementation of the HDPS procedure on Mini-Sentinel CDM detected more known positive associations than that on OMOP CDM. The SCCS method results were comparable on both CDMs. Differences in the implementation of the HDPS procedure between the two CDMs were identified; analytic model and risk period specification had a significant impact on the performance of the HDPS procedure on OMOP CDM.

Key Points

There are conceptual differences in the development of the Observational Medical Outcomes Partnership (OMOP) and Mini-Sentinel common data models (CDMs) and their related tools.

Conceptual differences in the specifics of the CDM structure and data representation had only a slight impact on identifying known safety associations in Humana data.

Differences in the implementation of analytic procedures across the CDMs can lead to strikingly different risk estimation in certain situations.

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Conclusions Differences were observed between OMOP and Mini-Sentinel CDMs. The analysis of both CDMs at the data model level indicated that such conceptual differences had only a slight but not significant impact on identifying known safety associations. Our results show that differences at the ecosystem level of analyses across the CDMs can lead to strikingly different risk estimations, but this can be primarily attributed to the choices of analytic approach and their implementation in the community-developed analytic tools. The opportunities of using CDMs are clear, but our study shows the need for judicious comparison of analyses across the CDMs. Our work emphasizes the need for ongoing efforts to ensure sustainable transparent platforms to maintain and develop CDMs and associated tools for effective safety surveillance.

1 Introduction

Since the US FDA Amendments Act of 2007, which required the FDA to create an active post-market drug safety surveillance system that leverages existing healthcare data from 100 million people by 2012 [1], there has been much interest in using data generated from routine clinical care and administrative transactions in international safety surveillance research. Numerous healthcare databases, with different properties, are useful for safety surveillance of marketed medical products [2]. At the same time, there is a trend to leverage multiple databases through distributed networks to facilitate surveillance research [3–6]. A key component to coordinating surveillance activities across many distributed networks is the use of a common data model (CDM). A CDM is not data per se, but rather the framework for extracting data from different sources, transforming those data into a standardized format, and then loading the data into a uniform data structure, thus allowing for execution of standardized analysis across a distributed network. Multiple CDMs have been developed and published, including the Observational Medical Outcomes Partnership (OMOP) CDM [7, 8] and Mini-Sentinel CDM [9] in the USA, and the exploring and understanding adverse drug reactions (EU-ADR) project CDM in the EU [10].

Of particular interest in terms of CDM development, OMOP and Mini-Sentinel were established after the US congressional mandate for a post-approval drug safety surveillance system. Even though these two initiatives were intended to support the common goal of the development and effective use of broad drug safety surveillance across healthcare databases, the resulting surveillance ecosystems have important differences. In this context, we define the surveillance ecosystem as the collection of components including the CDM architecture, technical documentation, analytical tools, policies, and the community of researchers and support personnel. In this definition, OMOP and Mini-Sentinel represent two different ecosystems with some overlapping and distinct goals that drive the development and underlying philosophy. In particular, the Mini-Sentinel program was charged with developing a national drug safety surveillance system under FDA contract, whereas OMOP had a methodological remit and focused primarily on the development and comparison of surveillance methods through a public–private partnership. Even though both OMOP and Mini-Sentinel involve a distributed network built around a CDM, their approaches in establishing their analytic architecture have important differences. OMOP focused on the development of a priori-designed methods intended to run on derived variables (drug and condition eras) for analytic efficiency, whereas Mini-Sentinel is based on a mix of generalized analytic modules and protocol-driven code. Standardized methods and vocabularies, such as those implemented in OMOP, may be more valuable for signal detection, whereas modular program analysis and protocol-based assessments supported by Mini-Sentinel may be most applicable to signal refinement and signal evaluation activities [11].

To optimize the value of a CDM-based drug surveillance ecosystem, there is a need to understand how underlying source data, CDM architecture, extraction, transformation and loading (ETL) processes, and analytic tools systematically influence how we interact with different surveillance systems and how we interpret study results. The purpose of this study was to evaluate and compare the two surveillance ecosystems with specific attention to the CDM and analytic tools. We have focused primarily on CDM applicability to signal detection and early signal refinement, where rapid search capability is paramount and widely deployed CDMs bring most potential benefit. The goals of this project were to (1) implement key parts of the OMOP and Mini-Sentinel ecosystems (i.e., CDM and analytic procedures); (2) describe key design differences between CDMs and analytic environments; (3) compare populations from source data that are captured in each CDM; (4) compare drug and health outcome cohorts identified between the two CDMs; (5) compare the performance and effect estimates from two analytic methods across OMOP- and Mini-Sentinel-implemented ecosystems; and (6) compare the performance and effect estimates from two analytic methods when standardizing data model inputs (identical patient cohorts) into the analytic procedures to understand the variation produced at the analytic procedure level.

2 Methods

2.1 Data Source and Common Data Model (CDM) Construction

This study was conducted using enrollment and administrative insurance claims data from a large US health plan, Humana, Inc. These data are collected to facilitate reimbursement and administration of health plan benefits. CDMs based on OMOP and Mini-Sentinel specifications were constructed using identical source data for commercial and medicare advantage prescription drug plan (MAPD) health maintenance organization (HMO)/preferred provider organization (PPO) insurance plan members covering service dates from 1 January 2007 to 31 December 2012.

2.1.1 Observational Medical Outcomes Partnership (OMOP) CDM Construction

The OMOP CDM was constructed following OMOP CDM Specifications version 4.0 and OMOP Standard Vocabulary Specification version 4.4 [12]. An overview of the OMOP CDM has been discussed elsewhere [13, 14]. The Standard Vocabulary is part of the OMOP CDM and is a fundamental tool developed by the OMOP team to enable standardization of data across disparate observational databases. To construct the OMOP CDM, source data were mapped to standardized OMOP "Concept IDs" through mapping provided in the Vocabulary. "Concepts IDs" are OMOP-defined unique identifiers that serve as the basis for standardized analysis using OMOP-developed analytical procedures. The OMOP CDM was validated using OMOP-developed tools including the Observational Source Characteristics Analysis Report ("OSCAR") and Generalized Review of OSCAR Unified Checking ("GROUCH"), as well as through direct comparison of the OMOP CDM to source data. "OSCAR" provides a systematic approach for summarizing data in OMOP CDM format, and "GROUCH" is a data anomaly detection tool developed by OMOP to look for and report potential data quality issues across all tables observed from the "OSCAR" summary.

2.1.2 Mini-Sentinel CDM Construction

The Mini-Sentinel CDM was constructed based on Mini-Sentinel specification version 2.1 [9]. While the Mini-Sentinel CDM also provides a common framework for representation of information across data sources, it is a "mixed" model where some data elements, such as sex and race, are standardized; however, unlike OMOP CDM, data elements such as diagnoses, medications, and procedures use native coding schema [e.g., *International Classification of Diseases, 9th Revision* (ICD-9), National Drug Code (NDC), Current Procedure Terminology (CPT), etc.] [5, 9]. For an overview of the Mini-Sentinel CDM, see Curtis et al. [5]. The Mini-Sentinel CDM conversions were validated using Mini-Sentinel Data Quality Review and Characterization Programs (version 3.0.1). In addition, the comparison between CDM data and source data also served a validation purpose.

2.2 Safety Endpoints, Drugs of Interest, and Comparator Drug Selection

Six drugs–outcome pairs were established a priori for examination of analytic procedure performance (indomethacin–acute myocardial infarction, ketorolac–gastrointestinal bleeding, benzodiazepines–hip fracture, valproic acid–acute liver injury, carbamazepine–acute liver injury, and amoxicillin–anaphylactic shock; see Table 1 for more details). Attempts were made to generate a varied list of pairs of importance in safety. Validation of the case definitions was outside the scope of this study; instead, pairs were selected from externally published reference sets.

The health outcomes for this study were selected based on the following criteria: (1) health outcomes representing clinically significant endpoints of common study as a safety outcome, with established positive associations with potential drugs of interest based on established reference sets [4, 14, 15]; (2) the endpoints had existing OMOP case definitions or a published Mini-Sentinel health outcome review; and (3) selected health outcomes would not be overly focused on OMOP-defined health outcomes or Mini-Sentinel health outcomes. In fact, we deliberately selected some health outcomes that were initially defined and extensively studied primarily in OMOP and other health outcomes that were instead well-studied and defined early in the Mini-Sentinel development cycle, to guard against any CDM-specific development with particular health outcomes in mind. Health outcome-specific coding definitions were based on reviews published by OMOP and Mini-Sentinel researchers [16, 17].

Drugs of interest were then selected as pairs for the outcomes based on the following criteria: (1) true positive association with the specified health outcome based on pre-established reference standards, specifically OMOP or EU-ADR reference sets with preference for drugs with a stronger study evidence base [4, 14, 15]; and (2) commonly recorded medication use in the Humana database, in order to minimize the risk of small case counts. Comparator drugs required for the HDPS method were also selected from negative control reference sets developed by the OMOP and the EU-ADR consortiums [4, 14, 15].

Table 1 Health outcome of interest, drug of interest, comparator drug, and source of identification for comparator drug [9, 14, 15]

Health Outcome of Interest	ICD-9-based definition	Drug of interest	Comparator drug
AMI[a]	Occurrence of at least one diagnostic code ICD-9 410* (Acute myocardial infarction)	Indomethacin	Loratadine
GI bleeding[a]	Occurrence of at least one diagnostic code (see Appendix B for full code list) AND hospitalization at date of diagnostic code	Ketorolac	Loratadine
Hip fracture[a]	Occurrence of at least one diagnostic code ICD-9 820* (Fracture of neck of femur)	Benzodiazepines	Lisinopril
Acute liver injury[b]	Presence of a primary ICD-9 hospital diagnosis code indicative of toxic hepatitis or acute liver failure (570, 572.2, 572.4, 572.8, V42.7, 573.3, 573.8)	Valproic acid	Fluticasone
Acute liver injury[b]	Presence of a primary ICD-9 hospital diagnosis code indicative of toxic hepatitis or acute liver failure (570, 572.2, 572.4, 572.8, V42.7, 573.3, 573.8)	Carbamazepine	Fluticasone
Anaphylactic shock[b]	ICD-9 code for anaphylactic shock (995.0)	Amoxicillin	Levothyroxine

AMI acute myocardial infarction, *GI* gastrointestinal, *ICD-9* International Classification of Diseases, 9th Revision, *OMOP* Observational Medical Outcomes Partnership

[a] Health outcome of interest from OMOP HOI reference set

[b] Health outcome of interest from Mini-Sentinel health outcome review

2.3 Analytic Methods for Testing

Standard analytic procedures have been developed by both OMOP and Mini-Sentinel communities for use with each CDM. This study applied two well-accepted, but fundamentally different, analytical methods for the control of confounding: one based on a new user cohort design with a comparison group when applying the high-dimensional propensity score algorithm (abbreviated as HDPS hereafter); and the other based on the univariate self-controlled case series design (abbreviated as SCCS hereafter). The two methods were selected because they have been widely used in pharmacoepidemiologic studies, and both have been implemented by at least one of the CDM communities in the form of standardized analytic procedures. These analytic procedures used on each CDM include user-defined parameters that allow the procedure to be configured to specific settings pertinent to the drug and outcome relationship under study or range of drugs and outcomes. The same parameter values were used for all of the individual drug–outcome analyses and none were selected to reflect drug–outcome-specific level design choices as would be done for a formal hypothesis testing study; rather, we focused on generic choices that would necessarily be required in a signal detection/rapid early semi-automated signal refinement step [18]. In safety surveillance there is a need to look at a wide range of drug–outcome relationships, and, as such, different time at risk definitions may be appropriate. In certain cases, a shorter surveillance window anchored to initiation of drug exposure may be appropriate (e.g., hypersensitivity reactions). In others, a variable surveillance window based on the duration of drug exposure may be appropriate. To determine whether our results were likely to differ by selection of a fixed versus variable time at risk definition, we chose to conduct our analyses using two time windows: (1) a variable risk period (drug exposure duration plus 30 days from the exposure end date); and (2) a fixed risk period (30 days from the initiation of the drug exposure). Continuous exposure was determined using a 30-day allowable gap for both CDMs.

2.3.1 High-Dimensional Propensity Score (HDPS)-Based Analysis

HDPS-based analysis procedures use high-dimensional proxy adjustment for confounders [19]. The propensity score is used to achieve comparability between exposed and comparison groups in cohort studies. The HDPS algorithm involves multiple steps to identify data dimensions (e.g., diagnoses, procedures, and medications), empirically select covariates for adjustment, estimate propensity scores, and use them for risk estimate adjustment through matching, regression model adjustment, or stratification [19]. Consistent with an ecosystem evaluation, we used the HDPS procedures developed by the OMOP and Mini-Sentinel user communities. A comparison summary of the methods and assumptions underlying Mini-Sentinel and OMOP HDPS-based analytic

Table 2 High-level summary comparison between the Observational Medical Outcomes Partnership and Mini-Sentinel High-Dimensional Propensity Score analytic procedure

	OMOP	MS
Relative complexity	Medium complexity (1 macro)	High complexity (multiple macros + external Java module)
Cohort	New user	New user
HOI	Incident	Incident (multiple definitions)
DOI/comparator drug	Drug era	Drug era produced by the analytical procedure
Risk period	Fixed or varying	Fixed or varying
Covariate selection	Empirical (HDPS)	Empirical (HDPS), pre-defined, or both
PS application	PS stratification, PS adjustment via logistic regression (PS as continuous or categorical variable)	PS matching, PS stratification (by PS deciles)
Effect estimation method/model	Logistic regression, Mantel-Haenszel method	Cox PH model
Effect estimates	Odds ratio	Risk difference, hazard ratio

DOI drug of interest, *HDPS* high-dimensional propensity score, *HOI* health outcome of interest, *MS* Mini-Sentinel, *OMOP* Observational Medical Outcomes Partnership, *PH* proportional hazard, *PS* propensity score

procedures is provided in Table 2. The Mini-Sentinel and OMOP HDPS-based analytic procedures are further described in the following sections.

2.3.1.1 HDPS-Based Analysis Procedure on OMOP CDM The OMOP HDPS procedure used in the study is comprised of a single SAS® (SAS Institute, Cary, NC, USA) macro program [27]. For the ecosystem comparison, we selected the propensity score adjustment using ten groups as indicator variables in logistic regression outcome model as this model was the focus of the OMOP application of the HDPS procedure [25]. For sensitivity analysis, we also implemented propensity score decile stratification using the Mantel-Haenszel method. Statistical significance was determined based on the lower 95 % confidence interval bound of odds ratio (OR) estimates. See Electronic Supplementary Material Table 1 for specific parameter values used in executing the HDPS procedure on OMOP CDM.

2.3.1.2 HDPS-Based Analysis Procedure on Mini-Sentinel CDM The Mini-Sentinel cohort-matching Prospective Routine Observational Monitoring Program Tool (PROMPT, version 1.0, 10 January 2014) module comprises a suite of modular SAS® macros that identify patient cohorts and perform effect estimation in a distributed data setting based on propensity score-matched new user cohorts [20]. Empiric selection of covariates was used to produce propensity scores as it is available in both the Mini-Sentinel and OMOP procedure, and, for the purpose of signal detection, automated variable selection procedures may be preferred. We selected the propensity score decile stratification using the Cox proportional hazard model for confounder adjustment. The PROMPT tool has multiple user-supplied parameters. To execute the tool on the Mini-Sentinel CDM, parameter values were selected to match, as much as possible, those utilized in the HDPS macro execution on the OMOP CDM (see Electronic Supplementary Material Table 1). Statistical significance was determined based on the lower 95 % confidence interval bound of hazard ratio (HR) estimates.

2.3.2 Self-Controlled Case Series (SCCS) Analysis Procedure

Univariate SCCS is a case-based method that considers one drug and one outcome relationship and only includes individuals who have experienced the outcome of interest and were exposed to the study drug in the analysis [21]. It does not require a comparator drug group as each patient included in the SCCS analysis experiences both exposed and unexposed periods; thus, a case acts as its own reference, which implicitly controls for invariant covariates. The focus of estimation is the relative incidence, which is the ratio of the rate of events in a given post-exposure period (at-risk period) to the rate of events during "not at-risk periods" (i.e., either unexposed periods or periods of exposure that exceed or precede the "at-risk period").

OMOP has published standard SAS® macro procedures to implement the SCCS method on the OMOP CDM. Mini-

Sentinel, on the other hand, had not published standard procedures for this method at the time this analysis was conducted. As a result, an "ecosystem" type of evaluation was not feasible for the SCCS method. Instead, we created a custom procedure that was applied to both CDMs to execute the SCCS analysis. The custom SCCS procedure followed the steps in SCCS implementation described by Madigan [22], with modifications to accommodate multiple risk periods and incident events. The same custom SAS® program was executed on both CDMs, and utilized a conditional Poisson model to estimate the association between the drug of interest and health outcome. Statistical significance was determined based on the lower bound of the 95 % confidence interval of the incident rate ratio (IRR) estimate.

2.4 Analysis

2.4.1 CDM Structural and Representational Comparisons

Structural and representational comparisons (i.e., comparisons of information captured and represented within each CDM environment) were based on comparing OMOP CDM version 4.0 to Mini-Sentinel CDM version 2.1, the most recent CDM versions at the time this study was initiated.

2.4.2 CDM Data Comparisons

Descriptive analyses were conducted to describe source codes unmapped to OMOP standard vocabulary and to compare data represented in each CDM. Individual drug and outcome cohorts were extracted from each CDM, and were compared between the two CDMs at both source code and OMOP "Concept ID" level. For the Mini-Sentinel CDM, drug and outcome cohorts were identified based on the source ICD-9 and NDC codes. For the OMOP CDM, drug and outcome cohorts were extracted using source codes (ICD-9 and NDC) as well as "Concept IDs". At the "Concept ID" level, health outcome cohorts were identified based on "Concept IDs" directly mapped to the specified ICD-9 codes as well as descendent "Concept IDs" associated with them. "Concept IDs" were first identified using ICD-9 diagnosis codes from the "Source_To_Concept_Map" table; the descendent "Concept IDs" were then identified from the "Concept_Ancestor" table; drug of interest cohorts were identified based on ingredients for all drugs of interest (ingredients were first identified from the "Concept" table based on drug names {Concept_Class = Ingredient and CONCEPT_LEVEL = 2}; drug "Concept IDs" were then extracted from the "Concept_Ancestor" table for the ingredient) except for Benzodiazepine, which was based on the "Concept ID" pre-defined by OMOP (Concept ID 600000005).

2.4.3 Analytic Method Performance Evaluation

The purpose of this analysis was to evaluate the performance of the HDPS-based and SCCS-based analytic procedures on each CDM in identifying a known association between the selected drug–outcome pairs. A summary performance score was calculated based on the statistical analysis results of the selected drug–outcome pairs and compared between the two CDMs. Specifically, this score was calculated as the number of drug–outcome pairs where the known association was correctly identified (i.e., statistically significant with lower bound of 95 % confidence interval >1) divided by the total number of drug–outcome pairs evaluated. This score was calculated per analytic method (HDPS-based, SCCS-based), risk period (fixed and variable risk period) and CDM (Mini-Sentinel, OMOP). It must be noted that this summary score is descriptive and should be interpreted with caution given the small number of pairs ($n = 6$) examined.

An intermediate step for the method testing was to extract drug–outcome cohorts created by each analytical procedure prior to the model estimation. Crude relative risk was estimated based on these cohorts to determine what, if any, impact the analytical procedure's application of the inclusion/exclusion criteria may have on the cohort selection. The crude relative risk was calculated as the incidence proportion in the drug of interest cohort divided by the incidence proportion in the comparator drug cohort (for the HDPS algorithm) or the incidence rate in the exposed period divided by the incidence rate in the non-exposed period (for the SCCS algorithm).

2.4.4 Secondary Analysis

We anticipated a priori that further work would be needed if primary analysis indicated that differences exist in the results derived from the analytic methods applied to each CDM, as well as the constituency of drug–outcome cohorts identified from each CDM. To further understand results from the primary analysis, a secondary analysis was conducted to force identification of identical drug–outcome cohorts from both CDMs prior to the analytic procedure execution. To construct identical drug–outcome cohorts, an identical set of source codes (ICD-9 diagnosis for health outcome, NDC for drug of interest) were utilized to extract cohorts from the Mini-Sentinel and OMOP CDM. The HDPS and SCCS analysis procedures were then re-executed for all drug–outcome pairs using these identical cohorts as the analytic dataset.

3 Results

3.1 CDM Data Elements and Representational Comparisons

Data for 7,668,027 patients in the Humana claims dataset were extracted, transformed, and loaded into the OMOP and Mini-Sentinel CDMs. There are 15 data tables for mapping and two aggregate tables (Condition Era and Drug Era) in the OMOP CDM version 4 and ten tables in the Mini-Sentinel CDM version 2.1. Table 3 provides a summary comparison of the OMOP and Mini-Sentinel CDM tables. Both CDMs capture the majority of critical non-cost-related data fields in the source database. OMOP CDM also captures drug and procedure cost data while Mini-Sentinel CDM does not. Certain data fields potentially relevant to some pharmacoepidemiological studies are missing from one or both CDMs. For example, discharge status is captured in the Mini-Sentinel CDM but not OMOP CDM, while drug exposure type (pharmacy, mail order, physician procedure, or from electronic health record, etc.) and prescribing provider ID are captured in OMOP but not in Mini-Sentinel CDM. Further, inpatient admission diagnosis, admission type, and whether an ICD-9 diagnosis was present on admission are not captured in either CDM. A summary of data fields that are not covered by one or both CDMs is provided in Electronic Supplementary Material Table 2.

Table 3 Summary of Observational Medical Outcomes Partnership and Mini-Sentinel Common Data Model tables

OMOP CDM	MS CDM[a]
Person	Demographic
Drug exposure	Dispensing
Condition occurrence	Diagnosis
Observation period	Enrollment
Observation	Laboratory, vitals (separate tables)
Procedure occurrence	Procedure
Visit occurrence	Encounter
Death	Death; cause of death
Drug cost	No analogous table present
Procedure cost	No analogous table present
Location	No analogous table present[b]
Provider	No analogous table present[b]
Organization	No analogous table present
Care site	No analogous table present[b]
Payer plan period	No analogous table present[b]
Drug Era	No analogous table present
Condition Era	No analogous table present

CDM common data model, *MS* Mini-Sentinel, *OMOP* Observational Medical Outcomes Partnership

[a] Based on OMOP CDM version 4.0 and Mini-Sentinel CDM version 2.1

[b] OMOP Provider, Care site, and Location tables did not have explicitly analogous Mini-Sentinel tables present; however, some elements of provider and care facility location were captured in the Mini-Sentinel CDM Encounter table. Similarly, Mini-Sentinel CDM had no explicit payer plan period table; however, some elements were captured in the Mini-Sentinel CDM Enrollment table

In terms of data representation, the major difference between the two CDMs is that OMOP CDM represents source data through OMOP standard vocabularies, such as SNOMED-CT (Systematized Nomenclature of Medicine—Clinical Terms) and RxNORM, while Mini-Sentinel CDM retains data in source code format. The decision to use a standardized vocabulary results in structural differences between the two CDMs. ETL conventions also contribute to differences in context. For example, the OMOP Drug Exposure table includes drugs documented via CPT and/or J-codes on medical claims, whereas the Mini-Sentinel Dispensing table does not. In Mini-Sentinel CDM, these drugs billed via medical claims (hereafter referred to as "procedure drugs") are found only in the procedure table. In addition, OMOP has derived data for drug era and condition era built into the CDM, while no similar tables are built into the Mini-Sentinel CDM.

3.2 CDM Data Comparisons

The comparison between source data and data captured in each CDM revealed that source data, Mini-Sentinel CDM, and OMOP CDM were identical at source code level for member count, member age and gender distribution, average number of conditions/procedures per member, and top ten conditions/procedures in the CDM (results not shown). Discrepancies were observed between source data and OMOP CDM data in "Concept IDs" due to unmapped source codes (see Fig. 1). About 2.2 % of the condition occurrence records were unmapped, which were predominantly V codes. Procedures had a much better mapping, with less than 0.01 % of procedure occurrence records unmapped. Drug exposure had approximately 2.6 % of records with unmapped source codes, where the most frequent unmapped drug codes were medical supplies (e.g., test strips, lancets) rather than therapeutic medications.

3.3 Health Outcome Cohort Comparisons

All five health outcome cohorts identified from Mini-Sentinel and OMOP using source codes were identical. When using OMOP "Concept IDs", the results between the two CDMs were similar for two cohorts (acute myocardial infarction and hip fracture) but substantially different for other health outcomes (see Table 4). These differences could result from several sources. First, there is no one-to-one mapping between the ICD-9 diagnosis code and

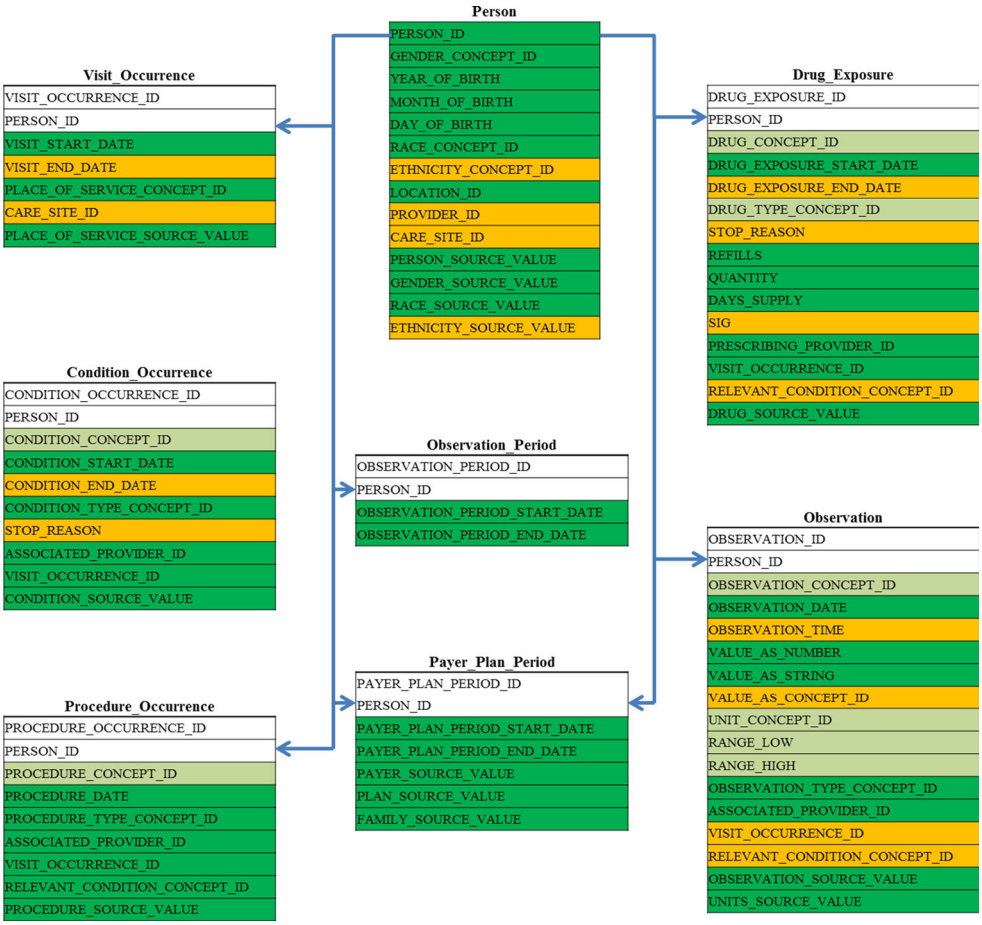

Fig. 1 Database heat map: overall mapping quality of the Humana database in the Observational Medical Outcomes Partnership (OMOP) common data model (CDM). *Dark green* complete mapping, *light green* incomplete mapping, *yellow* not available to map, *white* system generated. Note: selected Humana OMOP CDM data tables are included in this figure

Table 4 Health outcome of interest cohorts identified from Mini-Sentinel and Observational Medical Outcomes Partnership common data models (number of patients)

HOI	In MS CDM	In OMOP CDM	In both CDMs	In MS not OMOP	In OMOP not MS
AMI	166,930	166,442	166,442	488 (0.29 %)	0 (0.00 %)
Hip fracture	70,478	71,418	70,139	339 (0.48 %)	1279 (1.79 %)
Anaphylactic shock	7842	11,619	7842	0 (0.00 %)	3777 (32.51 %)
GI bleeding	77,411	85,289	76,538	873 (1.13 %)	8751 (10.26 %)
Acute liver injury	5005	15,481	4995	10 (0.20 %)	10,486 (67.73 %)

Cohort identified from OMOP CDM based on concept IDs in the condition occurrence table. MS CDM cohorts identified from the diagnosis table. Unique patient counts are reported

AMI acute myocardial infarction, *CDM* common data model, *GI* gastrointestinal, *HOI* health outcome of interest, *MS* Mini-Sentinel CDM, *OMOP* Observational Medical Outcomes Partnership CDM

OMOP "Condition Concept IDs" as OMOP uses SNOMED-CT as its basis for standardized "Concept IDs". For example, diagnosis code 572.8 (Other sequelae of chronic liver disease) was mapped to OMOP "Concept ID" 194984 (concept code 235856003, OMOP concept name "Hepatopathy"). However, this "Concept ID" also includes four other ICD-9 diagnosis codes in the OMOP standard vocabulary (571.8—Other chronic nonalcoholic liver disease, 571.9—Unspecified chronic liver disease without mention of alcohol, 573.8—Other specified disorders of liver, and 573.9—Unspecified disorder of liver). Consequently, patients with these four diagnosis codes were also included in the cohort when extracted based on "Concept ID" 194984. Second, health outcome cohorts were identified from Mini-Sentinel CDM based strictly on the source ICD-9 codes as compared to the use of "Concept IDs" in OMOP CDM, which also include descendent "Concept IDs". For example, the ICD-9 diagnosis code

Table 5 Drug of interest cohorts identified from Mini-Sentinel and Observational Medical Outcomes Partnership common data models (number of patients)

DOI name	In MS CDM	In OMOP CDM	In Both CDMs	In MS not OMOP	In OMOP not MS
Indomethacin	106,049	106,034	106,034	15 (0.01 %)	0 (0.00 %)
Ketorolac	42,556	470,723	42,556	0 (0.00 %)	428,167 (90.96 %)
Benzodiazepines	1,000,546	1,036,151	993,507	7039 (0.70 %)	42,644 (4.12 %)
Valproic acid	52,422	52,422	52,422	0 (0.00 %)	0 (0.00 %)
Carbamazepine	28,784	28,782	28,782	2 (0.01 %)	0 (0.00 %)
Amoxicillin	1,780,267	1,780,266	1,780,266	1 (0.00 %)	0 (0.00 %)

Cohorts identified from OMOP CDM drug exposure table based on concept IDs. cohorts identified from MS CDM dispensing table based on source codes (NDC). Unique patient counts are reported

CDM common data model, *DOI* drug of interest, *MS* Mini-Sentinel CDM, *NDC* National Drug Code, *OMOP* Observational Medical Outcomes Partnership CDM

specified for Anaphylactic Shock was 995.0, which was mapped to "Concept ID" 441202 (Other anaphylactic shock). This SNOMED-CT-based "Concept ID" has several descendants, which were also used to identify the cohort, resulting in a significantly larger cohort for anaphylactic shock in the OMOP CDM.

3.4 Drug of Interest Cohort Comparisons

At source code level, all six drug of interest cohorts were identical between the two CDMs. Using OMOP "Concept IDs", four cohorts had near-identical patient counts between the Mini-Sentinel Dispensing table and OMOP Drug Exposure table (see Table 5). The Ketorolac cohorts were substantially different between the two CDMs. One reason for this difference was that there was no one-to-one mapping between NDC codes (used in Mini-Sentinel CDM) and OMOP drug "Concept ID". More importantly, the OMOP Drug Exposure table included procedure drug codes [e.g., Healthcare Common Procedure Coding System (HCPCS), CPT, etc.]. When using ingredient "Concept IDs" to identify drug of interest cohorts from OMOP CDM, these additional "procedure drugs" filed as medical claims in the doctor's office were included in the OMOP drug of interest cohorts but not in the Mini-Sentinel drug of interest cohorts.

3.5 HDPS-Based Analytic Procedure Results

The Mini-Sentinel PROMPT cohort-matching tool required substantial computational resources. We encountered some technical difficulties in implementing the tool on three of the six drug–outcome pairs even after increasing Java memory to 1 GB per instruction [24]. As a result, the Mini-Sentinel HDPS procedure was executed for the three affected drug–outcome pairs (benzodiazepine–hip fracture, carbamazepine–acute liver injury, and amoxicillin–anaphylactic shock) using a restricted analytic dataset covering timeframe 1 July 2011 to 31 December 2012. While the same computational barrier did not occur using the OMOP HDPS-based procedure, to keep the results comparable the OMOP HDPS procedure was executed using data from an identical timeframe for the three pairs impacted by Java memory problems.

3.5.1 Fixed Risk Period

The results of executing each HDPS-based analytic procedure on their respective CDM using a fixed risk period are summarized in Fig. 2 and Table 6. These analyses suggest that the results between OMOP and Mini-Sentinel implementations were generally consistent when using the fixed risk period. The point estimate for the drug–outcome association (OR for OMOP implementation and HR for Mini-Sentinel implementation) were all in the expected direction (i.e., positive association between the drug of interest and health outcome); however, not all were statistically significant (three pairs were statistically significant in the OMOP implementation while four were statistically significant in the Mini-Sentinel implementation).

A number of differences were observed in the analytic datasets produced by the Mini-Sentinel and OMOP HDPS-based procedures (Table 6). Drug of interest cohort size was similar for indomethacin ($n = 69{,}682$ vs. 71,228) and valproic acid ($n = 22{,}083$ vs. 21,446), but substantially different for all others, in particular the Ketorolac cohort ($n = 30{,}322$ vs. 356,469). As reported in Sect. 3.4, this difference was primarily due to additional procedure drugs included in the OMOP cohort. The size of comparator drug cohorts identified by the Mini-Sentinel and OMOP analytic procedures was similar for loratadine but different for the rest of comparator drugs.

While investigating potential sources for differences in the extracted intermediate analytic datasets, it was observed that the inclusion and exclusion criteria implemented by the Mini-Sentinel and OMOP procedures were not identical. The OMOP procedure excludes patients

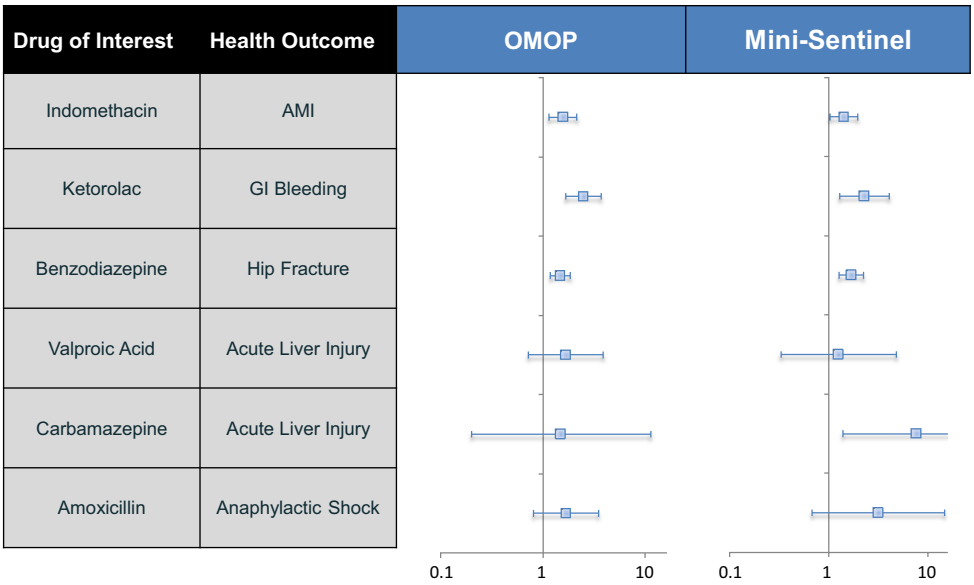

Fig. 2 Summary of High-Dimensional Propensity Score-based analytic procedure results: fixed risk period (30 days starting from index date). *AMI* acute myocardial infarction, *GI* gastrointestinal, *OMOP* Observational Medical Outcomes Partnership

whose drug of interest and comparator drugs exposure periods overlapped, while the Mini-Sentinel procedure excludes patients who had both drug of interest and comparator drugs on the index date only. The low incidence of some of the health outcomes examined made the difference more pronounced. For example, acute liver injury was a rare event, with only two cases identified for carbamazepine–acute liver injury cohort by the Mini-Sentinel procedure. The OMOP procedure initially identified the same two cases but excluded one from the analysis cohort as that patient not only took both drug of interest and comparator drugs but the exposure periods also overlapped. As a result, the Mini-Sentinel procedure reported a statistically significant positive association for this pair with an estimated HR of 7.7, while the OMOP procedure produced a statistically insignificant OR estimate of 1.6.

3.5.2 Variable Risk Period

The results of executing each HDPS-based analytic procedure using a variable risk period are summarized in Fig. 3 and Table 7. Compared to the results using a fixed risk period, the Mini-Sentinel procedure produced similar results for each pair in terms of the direction and statistical significance of the adjusted HR estimates; however, the OMOP procedure produced substantially different results with an adjusted OR <1.0 for four pairs (three were statistically significant), indicating a negative association between the drug–outcome pairs that was unexpected.

These results were further investigated to examine potential reasons for these unexpected results. We noted that the crude relative risk estimates were similar between both CDMs. In particular, the crude estimates for these four pairs were in the unexpected direction for both CDMs. In addition, these four pairs shared at least one commonality: the mean and median exposure time for each of the four drugs of interest were much shorter than their corresponding comparator drug (Electronic Supplementary Material Table 3), which means each drug of interest had a much shorter risk period than its comparator counterpart when a variable risk period was used.

3.6 SCCS Method Results

The custom SCCS macro was successfully executed for all six drug–outcome pairs on both CDMs (Table 8). For both the fixed and variable risk periods, the estimates were comparable and generally in positive direction (IRR >1) across both CDMs: with a fixed 30-day risk period, four pairs had statistically significant positive association on both CDMs; with a variable risk period, five pairs on OMOP CDM and four pairs on Mini-Sentinel CDM had statistically significant positive associations.

3.7 Method Performance

The overall performance of the HDPS-based and SCCS-based analytic procedures is summarized in Table 9. In this comparison, the OMOP HDPS analytic procedure had the lowest summary performance score (17 %) when a variable risk period was used, while the custom SCCS program applied to the OMOP CDM using a variable risk period had the highest performance score (83 %).

3.8 Secondary and Sensitivity Analyses

Secondary analyses were repeated for both the HDPS-based and SCCS-based analytic procedures with identical

Table 6 High-Dimensional Propensity Score-based analytic procedure results: fixed risk period[a]

Pair	HOI	DOI	Comparator drug	OMOP				MS			
				DOI[b]	Comparator[b]	Crude RR[c]	Adjusted OR[e] (95 % CI)	DOI[b]	Comparator[b]	Crude RR[c]	Adjusted HR[f] (95 % CI)
1	AMI	Indomethacin	Loratadine	71,228	38,642	1.42	1.57 (1.14–2.15)	69,682	35,414	1.34	1.43 (1.04–1.96)
2	GI bleeding	Ketorolac	Loratadine	356,469	36,776	1.83	2.49 (1.68–3.68)	30,322	35,902	1.42	2.30 (1.29–4.08)
3	Hip fracture[d]	Benzodiazepines	Lisinopril	224,663	244,253	1.42	1.47 (1.18–1.84)	154,235	137,353	1.36	1.70 (1.28–2.24)
4	Acute liver injury	Valproic acid	Fluticasone	21,446	504,665	3.14	1.67 (0.72–3.87)	22,083	417,545	3.34	1.26 (0.33–4.85)
5	Acute liver injury[d]	Carbamazepine	Fluticasone	5394	275,577	1.55	1.49 (0.20–11.24)	3912	188,659	13.78	7.72 (1.39–42.72)
6	Anaphylactic shock[d]	Amoxicillin	Levothyroxine	499,548	122,838	1.50	1.68 (0.81–3.47)	367,648	62,470	3.23	3.16 (0.68–14.80)

DOI drug of interest, *GI* gastrointestinal, *HOI* health outcome of interest, *HR* hazard ratio, *MS* Mini-Sentinel, *OMOP* Observational Medical Outcomes Partnership, *OR* odds ratio, *PS* propensity score, *RR* relative risk

[a] Fixed risk period 30 days starting from index date

[b] Unique patient counts are reported

[c] Based on the interim DOI/HOI cohort data produced in each procedure. RR was calculated as incident proportion in DOI/incident proportion in comparator cohort

[d] Both OMOP and MS used subset data for pairs 3, 5, and 6 (1 July 2011 to 31 December 2012)

[e] OR based on PS 10-group adjustment using logistic regression model

[f] HR based on PS decile stratification using Cox proportional hazard model

drug–outcome cohorts as input. The analysis results with the HDPS-based procedures were similar to the primary analyses reported in Sect. 3.5. Substantial differences remained between the Mini-Sentinel- and OMOP HDPS-based results when a variable risk period was used, even with identical cohort inputs. With the custom SCCS program, identical results for all six pairs were produced on the two CDMs.

Sensitivity analysis using the OMOP HDPS-based analysis procedure indicate that OR estimates based on propensity score stratification using the Mantel-Haenszel method were similar to those from propensity score adjustment using logistic regression model (see Electronic Supplementary Material Tables 5 and 6).

3.9 Other Comparisons

Computer execution times were recorded for each procedure The Mini-Sentinel HDPS-based procedure was the most resource intensive analysis, and the custom SCCS program was the least resource intensive. It took approximately half an hour for the custom SCCS macro to finish execution of all six drug–outcome pairs for both risk periods within each CDM. As a comparison, it took up to 41 h to complete execution of the Mini-Sentinel HDPS-based procedure for just one pair and one risk period (see Electronic Supplementary Material Table 4).

4 Discussion

4.1 Conceptual and Structural Differences

The conceptual differences in CDMs reflect differences in their design philosophy: Mini-Sentinel designed their CDM to reflect the concepts and granularity of source data and decided not to implement complex clinical mappings to standardized vocabularies since the underlying data systems are dynamic and prone to require frequent updating [5]. OMOP, on the other hand, developed their CDM with an emphasis on analytic efficiency and inclusion of data acquired from electronic health records in addition to the standard administrative data. Moreover, their CDM includes secondary data tables intended to aggregate patient-level medication exposures into drug eras and episodes of care into condition eras. Era aggregation also allows for the ability to distinguish periods of non-adherence from new episodes of treatment. OMOP also implemented standardized vocabularies to improve the integration of various types of data sources, e.g., problem lists from an electronic health record and diagnostic ICD-9 codes from administrative billing data were mapped into SNOMED-CT terms. OMOP standard vocabulary also

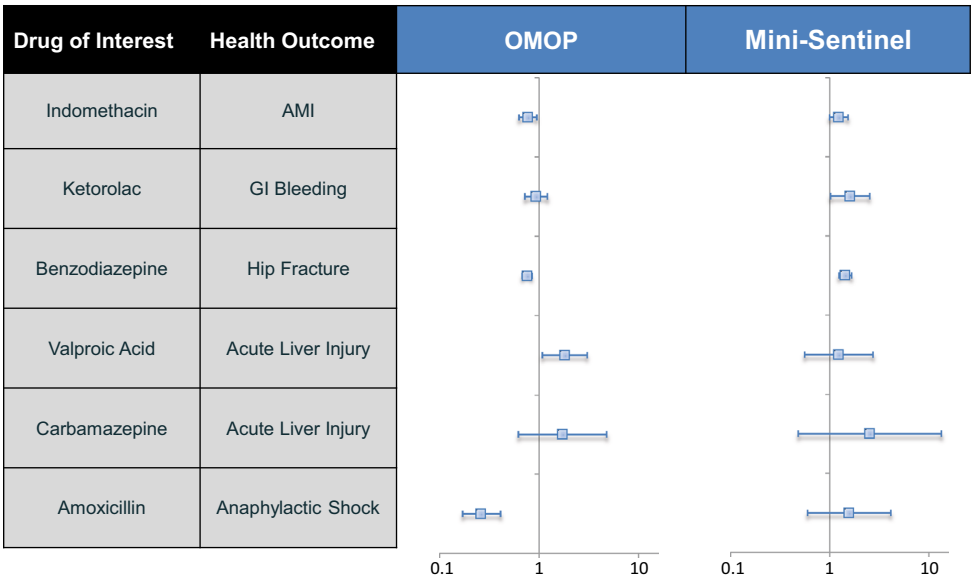

Fig. 3 Summary of High-Dimensional Propensity Score based analytic procedure results: variable risk period (drug exposure time plus 30 days). *AMI* acute myocardial infarction, *GI* gastrointestinal, *OMOP* Observational Medical Outcomes Partnership

incorporated key European terminologies and mappings to alternative terminologies such as the Anatomical Therapeutic Classification, Read codes, and the *Medical Dictionary for Regulatory Activities* (MedDRA®)[1] that are not represented in Mini-Sentinel CDM. OMOP designed their CDM in anticipation of access to clinical and cost data and inclusion of data based on local coding standards, whereas Mini-Sentinel appears to have made the decision to address such variability at the time of an analysis when necessary.

The results of this study demonstrated that source data, Mini-Sentinel CDM data, and OMOP CDM data were identical prior to any data aggregation or vocabulary processing. The OMOP CDM Drug Exposure table, however, included more members/records than both the Humana prescription source data and Mini-Sentinel CDM Dispensing table due to different handling of medication event data in the two CDMs. By design, the OMOP CDM represents medication events captured by procedure codes (e.g., J-codes, CPT codes) in the OMOP Drug Exposure table. In contrast, Mini-Sentinel CDM represents only medication events collected from outpatient pharmacy claims in its drug event table (Dispensing table); however, procedure drugs are represented in alternative data tables within the CDM (i.e., Procedure table). These differences in the CDM architecture are important when examining medications or treatments that may be office administered and may not be captured by outpatient pharmacy claims (e.g., vaccinations, injectable medications, etc.). It should be noted that differences in identifying drug exposure determination based on data representation in the two CDMs can be avoided if, for example, procedure-based drug administration is explicitly considered during development of a surveillance study plan when using Mini-Sentinel CDM. In a rapid signal detection environment, CDM use brings advantages and certain efficiencies, but also requires careful consideration of the underlying data structure and content.

Examining unmapped source codes in OMOP CDM revealed that there was information loss when source data were transformed into OMOP standard vocabulary, but most unmapped codes in this study had no or minimal impact on the active surveillance method testing.

Both CDMs capture the majority of critical data fields in the source database. There are certain data fields potentially important to some studies that are missing from one or both CDMs. For example, hospital admission source (referral, transfer, emergency room, etc.) and discharge status (died, transferred to another hospital, discharged to home, etc.) are captured in the Mini-Sentinel CDM but not OMOP CDM, while potentially relevant data fields in the source database related to inpatient utilization are not captured by either CDM. Other fields missing from both CDMs, such as admission diagnosis and health plan benefit information, may be less relevant to safety surveillance, but may have utility with extension into broader pharmacoepidemiology and pharmacoeconomics research. Designing an inclusive CDM ecosystem necessarily involves some compromises in terms of specific data elements that can or should be included. In the cases of certain surveillance activities or specific single protocol-driven

[1] MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH.

Table 7 High-Dimensional Propensity Score-based analytic procedure results: variable risk period[a]

Pair	HOI	DOI	Comparator drug	OMOP				MS			
				DOI[e]	Comparator[e]	Crude RR[d]	Adjusted OR[c] (95 % CI)	DOI[e]	Comparator[e]	Crude RR[d]	Adjusted HR[f] (95 % CI)
1	AMI	Indomethacin	Loratadine	71,137	38,564	0.76	0.77 (0.63–0.95)	69,682	35,414	0.71	1.24 (1.00–1.54)
2	GI bleeding	Ketorolac	Loratadine	356,078	36,488	0.79	0.93 (0.72–1.21)	30,322	35,902	0.61	1.61 (1.02–2.54)
3	Hip fracture[b]	Benzodiazepine	Lisinopril	212,616	236,532	0.71	0.76 (0.68–0.85)	154,235	137,353	0.55	1.44 (1.24–1.67)
4	Acute liver injury	Valproic acid	Fluticasone	20,867	503,454	3.09	1.82 (1.08–3.05)	22,083	417,545	5.20	1.24 (0.56–2.75)
5	Acute liver injury[b]	Carbamazepine	Fluticasone	5233	275,278	2.13	1.72 (0.62–4.79)	3912	188,659	6.89	2.54 (0.48–13.46)
6	Anaphylactic shock[b]	Amoxicillin	Levothyroxine	484,632	118,076	0.31	0.26 (0.17–0.41)	367,648	62,470	0.28	1.57 (0.60–4.15)

AMI acute myocardial infarction, *DOI* drug of interest, *GI* gastrointestinal, *HOI* health outcome of interest, *HR* hazard ratio, *MS* Mini-Sentinel, *OMOP* Observational Medical Outcomes Partnership, *OR* odds ratio, *PS* propensity score, *RR* relative risk

[a] Variable risk period = drug exposure time plus 30 days from the exposure end date

[b] Both OMOP and MS used subset data for pair 3, 5, 6 (1 July 2011 to 31 December 2012)

[c] OR based on PS 10-group adjustment using logistic regression model

[d] Based on the interim DOI/HOI cohort data produced in each procedure. RR was calculated as (incident proportion in DOI/incident proportion in comparator cohort)

[e] Unique patient counts are reported

[f] HR based on PS decile stratification using Cox proportional hazard model

Table 8 Self-controlled case series analytic procedure results

HOI	DOI	OMOP			MS		
		N^a	Crude IRR[b]	IRR (95 % CI)[c]	N^a	Crude IRR[b]	IRR (95 % CI)[c]
Fixed risk period[d]							
AMI	Indomethacin	6226	1.61	1.32 (1.18–1.47)	6240	1.61	1.32 (1.19–1.47)
GI bleeding	Ketorolac	10,534	3.01	2.47 (2.3–2.64)	844	2.99	2.39 (1.83–3.11)
Hip fracture	Benzodiazepines	23,602	1.67	1.43 (1.36–1.5)	22,082	1.44	1.23 (1.17–1.29)
Acute liver injury	Valproic acid	212	2.08	1.55 (0.94–2.57)	94	1.88	1.42 (0.67–3.02)
Acute liver injury	Carbamazepine	124	1.34	1.18 (0.54–2.57)	44	1.83	1.83 (0.64–5.27)
Anaphylactic shock	Amoxicillin	5066	2.13	1.82 (1.65–2)	3269	2.38	2.09 (1.86–2.35)
Variable risk period[d]							
AMI	Indomethacin	6226	1.51	1.34 (1.23–1.46)	6240	1.51	1.34 (1.23–1.46)
GI bleeding	Ketorolac	10,534	2.61	2.21 (2.07–2.37)	844	2.35	2.02 (1.58–2.58)
Hip fracture	Benzodiazepines	23,602	1.25	1.3 (1.25–1.35)	22,082	1.2	1.19 (1.14–1.23)
Acute liver injury	Valproic acid	212	1.69	1.76 (1.22–2.53)	94	1.52	1.55 (0.88–2.74)
Acute liver injury	Carbamazepine	124	1.08	0.96 (0.56–1.64)	44	1.03	0.92 (0.38–2.21)
Anaphylactic shock	Amoxicillin	5066	1.93	1.66 (1.52–1.81)	3269	2.15	1.91 (1.71–2.12)

AMI acute myocardial infarction, *DOI* drug of interest, *GI* gastrointestinal, *HOI* health outcome of interest, *IRR* incident rate ratio, *OMOP* Observational Medical Outcomes Partnership

[a] Unique patient counts are reported

[b] Calculated based on interim data before the estimation model

[c] Created from the conditional Poisson regression model of the custom code

[d] Fixed risk period covered the time period 30 days from the index date; variable risk period covered the time period from the index date to end of drug exposure plus 30 days

Table 9 High-Dimensional Propensity Score and Self-Controlled Case Series analytic procedure performance summary[a]

Method	Risk period	OMOP CDM performance score (%)	MS CDM performance score (%)
HDPS	Fixed	50	67
	Variable	17	50
SCCS	Fixed	67	67
	Variable	83	67

DOI drug of interest, *HDPS* high-dimensional propensity score, *HOI* health outcome of interest, *LBCI* lower bound of the confidence interval, *MS* Mini-Sentinel, *OMOP* Observational Medical Outcomes Partnership

[a] The performance score was calculated as number of DOI–HOI pairs where the positive association was correctly identified (determined by whether the estimated 95 % LBCI >1)/total number of pairs tested

studies, access to raw source data may be necessary or preferred.

4.2 Cohort Identification

In terms of drug–outcome cohort identification, results indicate that three health outcome cohorts and two drug of interest cohorts had quite substantial differences in cohort size (>10 % in number of patients or records) and constituency (e.g., 15 extra ICD-9 diagnosis codes in OMOP anaphylactic shock) between Mini-Sentinel and OMOP CDMs. These differences relate to multiple factors (e.g., CDM structure, such as inclusion of procedure drug codes in OMOP Drug Exposure table, information loss from source data to CDM), but primarily in this study are the result of the different underlying methodology for identifying cohorts using the OMOP standardized vocabulary compared to the direct source code identification process used on the Mini-Sentinel CDM.

4.3 Analytic Method Performance

Overall, Mini-Sentinel HDPS-based procedure on Mini-Sentinel CDM had higher performance scores than OMOP HDPS-based procedure on OMOP CDM, and the SCCS method produced a comparable score on both CDMs. Key study design features such as risk period had a significant impact on the results, especially when a variable risk period was used with the OMOP HDPS-based procedure. Differences in the statistical models used for risk estimation likely account for the differences observed when the variable risk period was used. The Mini-Sentinel HDPS-based procedure used a Cox proportional hazard model that considers time to event, while the logistic regression model used in the OMOP HDPS-based procedure did not account

for the varying exposure time between the study and comparator drugs. We observed substantial differences in the mean and median exposure time between the chosen drugs of interest and their comparator drugs. The choice of logistic regression model in the OMOP HDPS-based procedure without accounting for a differential follow-up length between the drug of interest and the comparator group gives patients in the group with longer exposure (i.e., comparator group in this study) greater opportunity for the events. The results using the Mantel-Haenszel method were similar, which also supports the finding above. Sensitivity of the risk estimate to comparator drug selection and unexpected directionality of association under certain circumstances of comparator drug specification have been reported in previous research with the OMOP HDPS procedure [26]. It should be noted that the comparator drugs were selected from pre-established negative control lists, and were not based on similarity to the drugs of interest. It is possible that the analytic procedures would perform differently if alternative comparators were selected based on other criteria, e.g., a common indication with the drug of interest, indicated population, or similar utilization patterns between the drug of interest and comparator drug. However, as comparator drugs were identical across both CDMs, such selection supports the comparative assessment of both CDMs and analytics, the primary purpose of this study.

We observed that known safety issues when the health outcome was a rare event (e.g., acute liver injury and anaphylactic shock) were identified by neither the HDPS nor SCCS procedures. This finding is consistent with previous research indicating that identification of drug–outcome associations can be compromised in the setting of rare health outcomes of interest, such as acute liver injury [25], although large databases or networks of databases may circumvent this problem.

Finally, there are differences in inclusion/exclusion criteria implemented in the OMOP and Mini-Sentinel HDPS-based procedures. For example, the OMOP implementation excludes patients whose drug of interest and comparator drug exposure periods overlap. Patients who start on the drug of interest and later become exposed to the comparator drug, while still exposed to the drug of interest, are excluded from this analysis. Excluding patients from analysis based on future events could be a potential source of selection bias and may impact the validity of the analysis results.

4.4 Secondary Analysis

Secondary analysis forcing identical drug–outcome cohorts yielded similar results for the HDPS-based procedures. By removing differences in cohort make-up resulting from the subject selection process, these series of analyses help isolate the impact of differences in the analysis procedures from differences in the cohort identification. While these results may suggest that the difference in the HDPS findings between the two CDMs are likely attributed to implementation of the analytic procedures rather than the CDMs themselves, we caution readers that differences in CDMs may not easily be untangled from the implementation of analytic procedure. For example, differences in HDPS results may arise from differences in confounding control as a result of differences in covariate coding intrinsic to each CDM (i.e., "Concept IDs" on OMOP CDM vs. ICD-9 codes on Mini-Sentinel CDM).

The identical results of the SCCS testing across CDMs, using identical analytic procedures and risk estimation models, further suggests that the differences in the nature of the CDMs themselves did not overall have a substantial impact on results.

4.5 Other Elements in the Ecosystem

Our assessment of the Mini-Sentinel and OMOP CDMs indicated that each CDM and its related ecosystem have its strengths and limitations. While standardization of data structure, vocabulary, and analytic programs facilitate analyses across multiple databases in a distributed network [26], it is important for researchers to be aware of the implications when interpreting results. Having an infrastructure ready to build a CDM is one of the keys to ensuring a successful implementation of the CDM construction and its application for active surveillance. Updating and maintenance of CDMs and their related tools, software, and documentation is important and yet challenging. In particular for the OMOP CDM, frequent updating of standardized vocabulary documentation is necessary. Standardized vocabulary may, however, be advantageous when healthcare billing standards vary across potential data sources or national boundaries where different coding systems are used [Read in the UK; *International Classification of Diseases, 10th Revision* (ICD-10) in Europe; ICD-9 in the USA], in the setting of migration from one billing standard to another (e.g., migration from ICD-9 to ICD-10), or when incorporating non-claims-based data sources such as electronic medical records.

Training for appropriate use of CDMs, and in particular the process of identifying outcomes and drugs of interest using standardized vocabulary, the appropriate use of CDM validation tools, and implementation of analytic procedures will help ensure appropriate use of CDMs. Clear and publically available up-to-date documentation is necessary to ensure broad usability and consistent implementation of CDM architecture and analytic tools. In particular, documentation of validation tools/programs, including guidance

in interpretation of output, is necessary in situations where a formalized relationship with a central coordination center may not exist. Likewise, sufficiently detailed documentation of analytic procedures is necessary to ensure appropriate implementation of analytic methods and interpretation of findings.

4.6 Future Work and Study Limitations

Future work to expand assessment of CDMs is recommended, and should include assessment of analytic procedure performance using a greater number of drug–outcome pairs and diversity of the source database. In particular, the evaluation of the robustness of CDMs and their associated analytical procedures to data heterogeneity is necessary. The limitations of the study are important to note. In particular, data for this study were sourced from one health plan, and the results may not be generalizable to other data sources or data environments. In the current study, use of data from a single source is also a potential strength, in that this reduces the impact of data heterogeneity. Also, the use of an administrative (billing) data source does not provide insights into the use of these CDMs with other data sources that can provide different perspectives, such as electronic health records or patient-reported outcomes.

Only six drug–outcome pairs were tested to assess the performance of the two active surveillance methods so the testing results should be interpreted with caution. For this study focused primarily on comparative assessment of CDMs for signal detection and early signal refinement using a large claim database, we did not specifically examine the study power for each drug–outcome pair. It is possible that some pairs may be underpowered in the Humana database. Comparator drugs for this study were chosen from established negative control references, which may represent different populations on the exposed and comparator medications. As discussed previously, however, such selection still supports the comparative assessment of both CDMs and analytics as comparator drugs were identical across both CDMs. We applied published health outcome definitions that only used diagnosis codes and did not use procedure or laboratory data. Finally, the safety surveillance landscape is rapidly evolving, and updated versions of CDMs, related tools, and analytic procedures are under frequent revision. For example, at the time that this research was conducted, there was not a tool distributed by the Mini-Sentinel community to implement the SCCS method, and thus we applied a custom SCCS method on Mini-Sentinel CDMs for comparative assessment with OMOP CDM. In the time since this research was completed, a Mini-Sentinel implementation of the SCCS has been released and OMOP CDM has progressed to version 5.0. Within the context of a rapidly evolving field, the focus on philosophical differences underlying a CDM environment makes this research less time sensitive, as these philosophical differences are maintained through consequent updates of the CDMs and supporting tools.

5 Conclusions

There are conceptual differences in the development of the OMOP and Mini-Sentinel CDMs. The analysis of both CDMs at the data model level indicated that such conceptual differences had only slight but not significant impact on identifying known safety associations. Our results show that differences at the ecosystem level of analyses across the CDMs can lead to strikingly different risk estimation, but this can be attributed primarily to the choices of analytic approach and their implementation in the community-developed analytic tools. Both the OMOP and Mini-Sentinel CDM models convert source data from different formats into a standardized data structure, facilitating their use in a variety of research settings including distributed safety surveillance networks. Such networks allow for rapid drug safety assessments, leveraging observational data from a wide range of sources. Multiple analytical tools have also been developed for use with each CDM; however, use of these tools requires detailed understanding of the structure and contents of the particular CDM, the underlying data, the analytics involved, and the impact of various input parameters to the analytic procedures. The results of this study suggest that comparisons of output from the Mini-Sentinel CDM and OMOP CDM, even in the setting of applying ostensibly similar analytical methods, needs to be done cautiously and judiciously. Future work to expand the assessment of both CDMs, including analytic procedures on the CDMs using more drug–outcome pairs on other claims or electronic healthcare databases, are recommended.

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Conflict of interest Yihua Xu, Brandon Suehs, Keran Moll, and Margaret Pasquale are employees of Comprehensive Health Insights, a wholly owned subsidiary of Humana. Brandon Suehs is a stockholder of Humana. Vinit Nair is an employee of Comprehensive Health Insights, and serves as the primary investigator from Humana

for both the Observational Medical Outcomes Partnership and the Mini-Sentinel program. Xiaofeng Zhou, Qing Liu, and Andrew Bate are employees and stockholders of Pfizer Inc. Abraham Hartzema, Michael Kahn, Brian Sauer, and Yola Moride received consulting fees and travel expenses in connection with providing input on the design of the study and interpretation of results.

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