

Final OMOP Study Report

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Department of Veterans Affairs
Center for Medication Safety

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I. Introduction

This is the final report of the VA Center for Medication Safety (VAMedSAFE) for the Observational Medical Outcomes Partnership (OMOP) project.

This report includes the following sections: 1) Introduction/background of the VAMedSAFE program, 2) Data characteristics of the study population, 3) Performance evaluation of methods, and 4) Process and lessons learned from participating in the OMOP project.

1. Background of VAMedSAFE

The VA Center for Medication Safety (VAMedSAFE) was initiated as a Patient Safety Center of Inquiry and was established in October 2003 through a grant co-funded by The VA National Center for Patient Safety and VA Pharmacy Benefit Management Services (PBM). VAMedSAFE was implemented to improve the safety of drug prescribing practices and medication administration for veterans receiving treatment in the Department of Veterans Affairs healthcare system thereby enhancing patient safety. VAMedSAFE has developed and implemented a programmatic structure whose primary goals are dedicated to identifying, tracking, and reducing preventable adverse drug events (ADEs). The tools used to accomplish the goals of VAMedSAFE include a comprehensive pharmacovigilance program which conducts postmarketing medication surveillance using VA's rich series of integrated databases. These databases are used to identify, strengthen and confirm potential ADE signals. VAMedSAFE's Risk Reduction Program is part of VA's pharmacovigilance program and was initiated to intervene upon preventable ADEs. In addition to the comprehensive pharmacovigilance program, VAMedSAFE provides drug safety information to providers through the Medication Safety Information/Education program. VAMedSAFE's efforts have aided in VA's decision making process on drug safety and directly intervened at the provider and patient level to reduce potential adverse medication events.

The VA Center for Medication Safety has also developed substantive collaborations with other entities and research groups inside and outside VA to promote and/or advise on drug safety. These relationships include: (1) National Center for Patient Safety and VA's Patient Care Services, (2) VA's Office of Quality, Safety and Performance, (3) VA Health Services Research Centers of Excellence, (4) The Food and Drug Administration, (5) AHRQ DeCIDE Networks, and (6) Center for Health Statistics at University of Illinois at Chicago.

2. VA Data Descriptions and Quality

General Overview

We have access to the National Patient Care Database (NPCD) that consists of the medical and clinical databases for all patients treated in the Veterans Health Administration branch of the VA providing health care services to over 5.5 million individuals a year. Data sources include all services provided at the system's 150 medical centers, approximately 1,000 ambulatory care and community-based outpatient clinics, 131 extended care facilities, and several comprehensive home care programs.

The NPCD data files contain detailed demographic data as well as information about hospitalizations and outpatient visits that occur within the VA system. All inpatient visits contain a primary diagnosis code in the International Classification of Disease (ICD-9-CM) and include all secondary diagnoses. All procedures conducted during an inpatient stay are also coded with ICD-9-CM procedure codes. Outpatient visit data contain information on a primary diagnosis and up to 9 secondary diagnoses per physician-patient encounter. Procedures provided in the outpatient setting are identified using CPT-4 procedure codes. There is one observation for each inpatient stay and each outpatient clinic visit. As many as 11 ICD-9 diagnoses are available.

Prescription drug utilization for all Veterans filling their prescriptions in VA is available in the Pharmacy Benefit Management (PBM) Services database. All records of prescription drugs dispensed in the VA since fiscal year 1999 (October 1, 1998) to the present are captured in this database. The data include detailed information such as drug name, total quantity, dosing instructions, day supply, type of prescription fill, and service date.

Separate data sets that contain laboratory test results and costs data are available from FY 2003 to the present. Also available is the Beneficiary Identification Records Locator System (BIRLS), the VA's mortality file. The death dates in the mortality database have extremely high accuracy (97.6% are accurate to the exact date) when compared with the death dates from the National Death Index.²

The VA datasets have been used extensively for medication safety efforts and research. Prescription databases and disease coding for many diagnostic codes have been extensively evaluated in VA for accuracy and quality.¹⁻⁷ All patients are identified by a VA assigned unique patient identifier which allows records to be merged at the unique patient level in order to be evaluated. In addition, medical charts are readily available to validate outcomes to confirm diagnosis when needed. Lastly, the datasets are readily accessible and are used on a daily bases as part of the Center for Medication Safety efforts.

Data Quality and Integrity for OMOP Study

All data are extracted from the centralized administrative databases. The databases are locked, remain behind a firewall and are not subject to changes. As stated previously, VA data are assessed for accuracy and quality. For specific projects however, individual data must also be reviewed. The integrity of prescription data as well as data obtained from NPCD should be assessed prior to every analysis.

At the time of data extraction we check the data for medical diagnostic codes, drug names and their classes, the dates of drug release, and dates of visit or admission. To assess data integrity for prescriptions a frequency count on the number of prescriptions is conducted by month to determine if the number of prescriptions changes dramatically over time. If the numbers are substantially different this would represent an error in data extraction. In order to assess the integrity of other variables such as diagnoses, procedures and visit dates we have access to patient records. Although we have access to records for data verification it is not done for every study as a standard practice. We do conduct however, record validation on a study by study basis or in the case of rapid analysis to confirm that a specific outcome is accurately coded and can be assessed.

For the OMOP study we followed our set procedures of checking data for missing visit/admit dates. As standard practice in our analyses we only exclude observations with missing visits or admission dates. We cleaned and verified the Date of Birth (DOB) and Date of Death (DOD) for our Common Data Model (CDM) by using multiple VA data resources. Also to be HIPPA compliant, adjustments were made for the DOB for patients born on or before 1920. We did not use multiple resources to validate the Race Field due to time constraints and to avoid further delay of the project. Also, if there was care after the study end date, (9/30/2009) the patients were assigned an end date of 9/30/2009. No other truncation was applied to the data.

3. Selection of OMOP Study Population

The OMOP study population was created from the PBM prescription database that contained prescriptions for patients who received Statin treatment in the VA between October 1, 2004 and September 30, 2009. Patients who received Statin treatment and who had at least one diagnosis (i.e., at least one inpatient or outpatient clinical visit) in the fiscal year (FY) 2005-FY 2009 period were included in the study. The Statin cohort has been a part of an ongoing project for internal signal generation efforts and was extended to the OMOP project.

II. OMOP Data Characteristics

1. GROUCH Report

After the creation of the CDM, we followed the OMOP guidelines and ran Observational Source Characteristics Analysis Report (OSCAR) and national history analysis (NATHAN) on our model. The Generalized Review of OSCAR Unified Checking (GROUCH) report was produced based on our run by OMOP. This report was a great help in assisting us in identifying and correcting errors in the CDM, identifying anomalies and in describing why our database was different from that of the Community. Since GROUCH perceived our CDM in comparison to the Community, the CDM itself was useful in allowing us to assess our data in direct comparison.

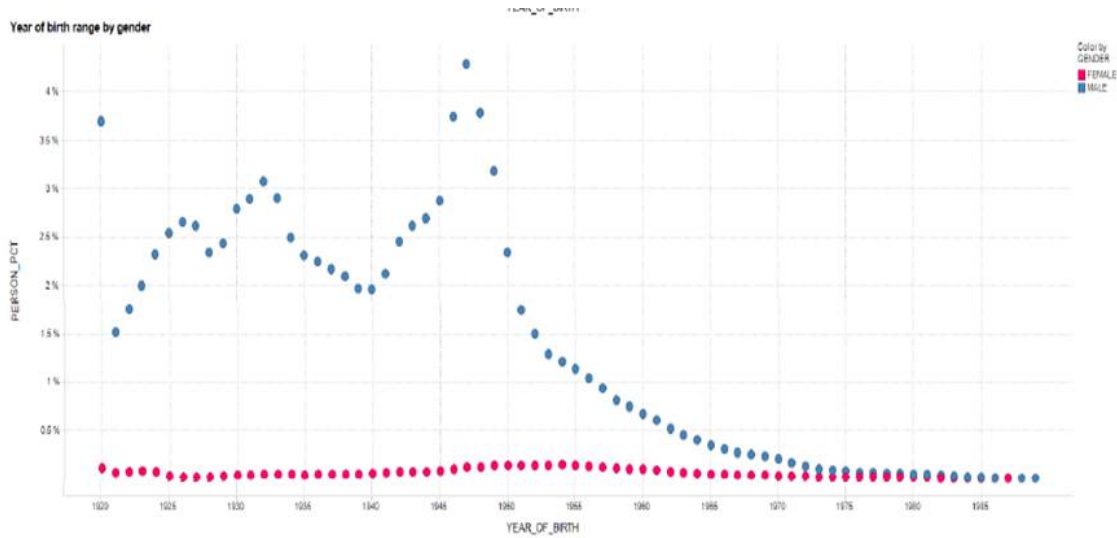
For the OMOP project, data were extracted from various VA data sources (Rx database, NPCD, and VA Vital Status Files). Date of birth, date of death, prescription day supply, and some of the lab values were reviewed and validated prior to creating the final datasets.

Some of the major anomalies identified in the GROUCH report were 1) more males than females, 2) the significant difference between female and male ages, 3) surge in births for 3 years between 1955-1968 as shown in Figure 1, and 4) almost no data for drugs for 3 months (4/2007 – 6/2007).

Identifying and assessing these kinds of anomalies is very important as it assisted us in understanding the individual data and helped assure that the data were correctly converted into the Common Data Model (CDM). Specifically, we were able to identify a gap in raw data for 3 months. After a thorough assessment we determined that 3 months of data were not properly transferred from the SQL database to SAS. Without the GROUCH report, this error may not have been identified.

Again, the use of GROUCH after the data were converted into CDM was very useful. In fact, if we had the ability to generate a GROUCH report at our site as a first quality check it would be extremely beneficial in giving us an expeditious data snapshot to assess initial outputs. As a result of the GROUCH report we changed some of the invalid dates of birth and prescriptions with days supply that were inaccurate (any Rx with greater than 180 days) in our OMOP dataset.

Figure 1: Percentage of person by YEAR of Birth and gender



2. Source Population

There are more than 23 million Veterans in the U.S. Of these, approximately 8 million are enrolled in the VA healthcare system. Over 5 million of these Veterans seek care within the Veterans Health Administration (VHA) on a consistent basis. Once the patients enter the system they are followed closely within the VA healthcare system through their life time. Many of the Veterans that use the healthcare system have multiple co-morbidities, increased mental illnesses and lower socioeconomic status. The population is predominantly male and approximately 40% are 65 years or older.

A large number of elderly Veterans who are eligible to use VA are also eligible to use Medicare for their health care. Dual use for the elderly has been estimated as high as 54% among surgical patients⁸ and about 30% for outpatients.⁹ In FY 2008, approximately 40% of patients had dual coverage with Medicare. Although patients 65 years and older can be easily identified as dual care users there is not good documentation to identify younger Veteran patients with dual insurance. All Veterans that use the VA healthcare system are eligible for prescription coverage under the VA’s comprehensive medical care plan. Even those Veterans with dual insurance are eligible for drug coverage through VA. Due to the lower prescription copayment for Veterans and in many instances no co-payment, Veterans obtain the majority of their medications through the VA system.¹⁰

Table 1 shows age and gender distributions for the United States (US) and Veteran populations. With the addition of Operation Enduring Freedom and Operation Iraqi Freedom, younger Veterans are entering the VA healthcare system. The female population has increased in recent years with an average age lower than that of male Veterans. This is better illustrated by Figure 2.

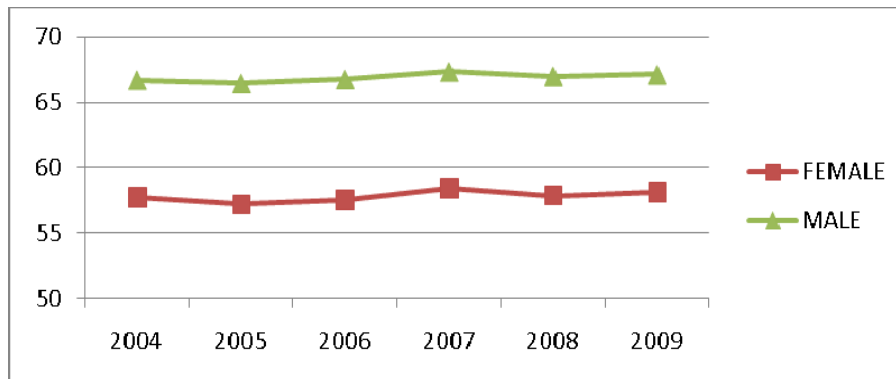
Table 1: Distribution of Age and Gender for General US and VA Population

Sex	All US Population(> 18 years)		Non-Veterans
		Veterans	
Male	48.5%	93.1%	43.4%
Female	51.5%	6.9%	56.6%
Age			
18 to 34 years	30.7%	8.1%	33.3%
35 to 54 years	38.1%	26.8%	39.3%
55 to 64 years	14.4%	25.4%	13.2%
65 to 74 years	8.7%	18.6%	7.5%
75 years and over	8.1%	21.2%	6.7%

* Source-- U.S. Census Bureau, 2005-2009 American Community

Survey (http://factfinder.census.gov/servlet/STTable?_bm=y&-geo_id=01000US&-qr_name=ACS_2009_5YR_G00_S2101&-ds_name=ACS_2009_5YR_G00_&-redoLog=false)

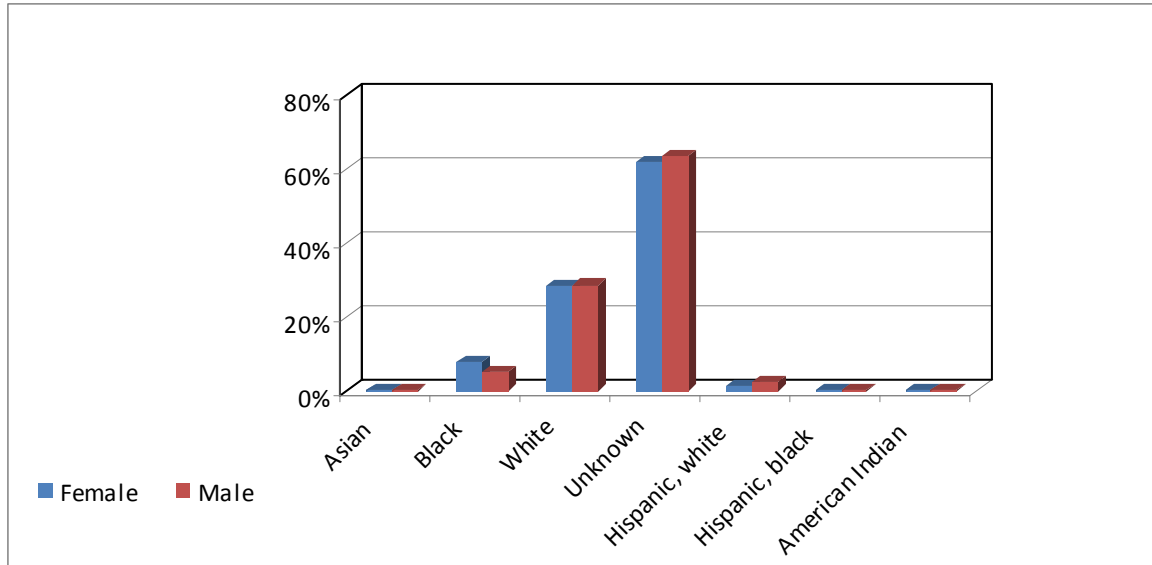
Figure 2: Average AGE by gender distribution over Study period



Since 2003 the VA started to collect self-reported race in compliance with a new federal guideline. The patient is given 7 race fields to choose from. They may choose more than one option to suggest their lineage in the best possible way. The collection of race information is not mandatory and thus the race variable contains the most missing values unless matched and corrected using multiple files and data

sources. We used a race variable from one specific database to create the CDM. This may have caused almost 60% of our race variable to be categorized as unknown (see Figure 3). As part of a larger ongoing project we have recently created a more complete race variable combining race information from multiple VA data sources that can be used on every project versus developing an updated race file for independent studies.

Figure 3: Race Distribution by Gender



The GROUCH report raised questions about the number of drug exposures and condition occurrences. As described, our population is older and sicker than the general population (mean ages for male and female for the study population are 69.6 and 60.6 years old, respectively), the number of drug exposures or condition occurrences in the VA population is therefore expected to be higher compared to most of the other distributed partners. This also caused our CDM to have more records and observations per patient. These can be seen in Figure 4.

Figure 4: Records per Person by Source (Median)

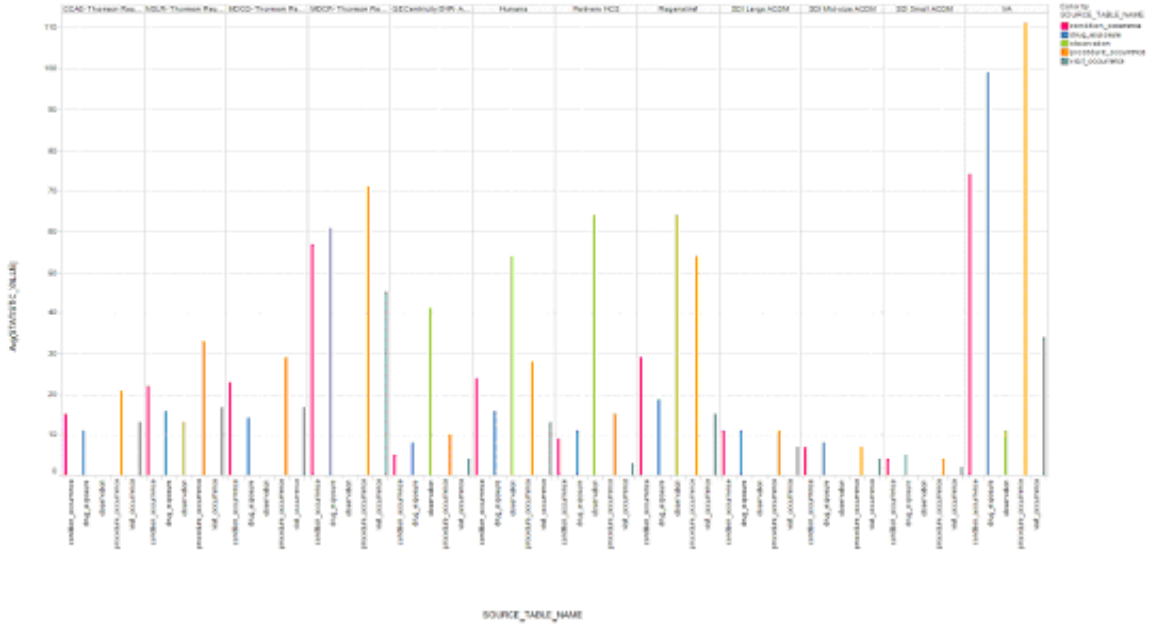


Figure 5 displays the number of records over time. The number of condition occurrences, drug exposures, procedure occurrences, and visit occurrences increases over time.

Figure 5: Number of Records Over Time

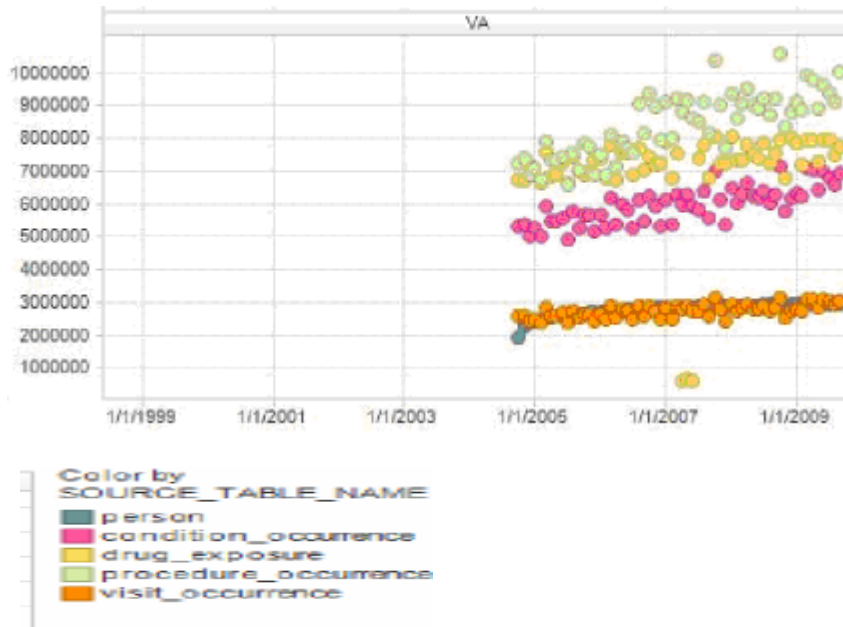


Figure 6 presents the observation period length over time. The mean and median lengths are similar while the other sources have a large variation. The observation period length was longer for VA compared to the other sources. This is most likely due to the fact that a patient is less likely to leave once entering the VA system. In fact, most Veterans once they enter the system remain until death. There were no differences in the length of observation periods by gender in the VA system. The observational period length by age is shown in Figure 7. Note that there was a large drop in the observation period length in the age group 60 to 68 years old the reason for which is currently being assessed.

Figure 6: Observation Period Length

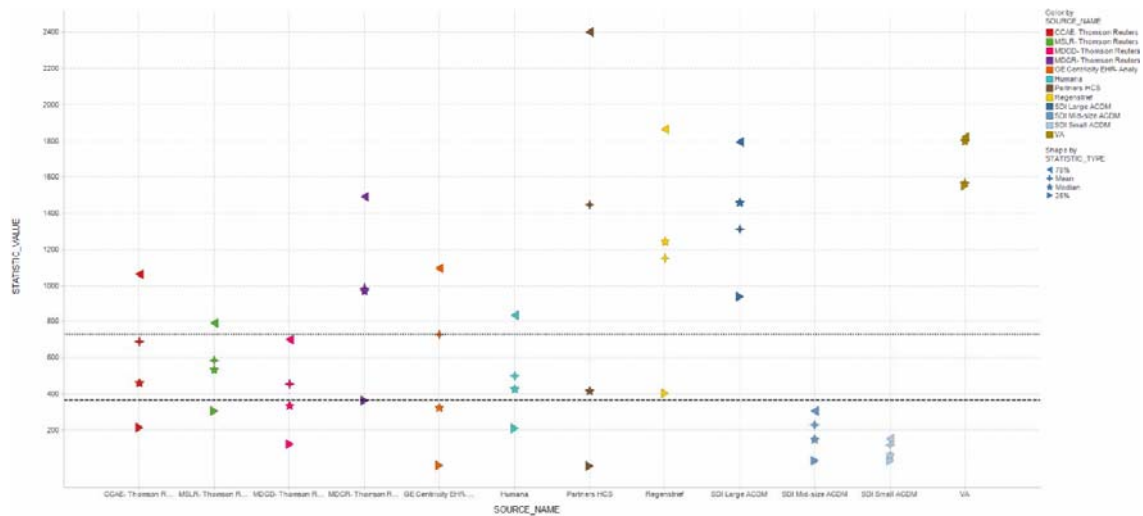


Figure 7: Observation Period Length by Age

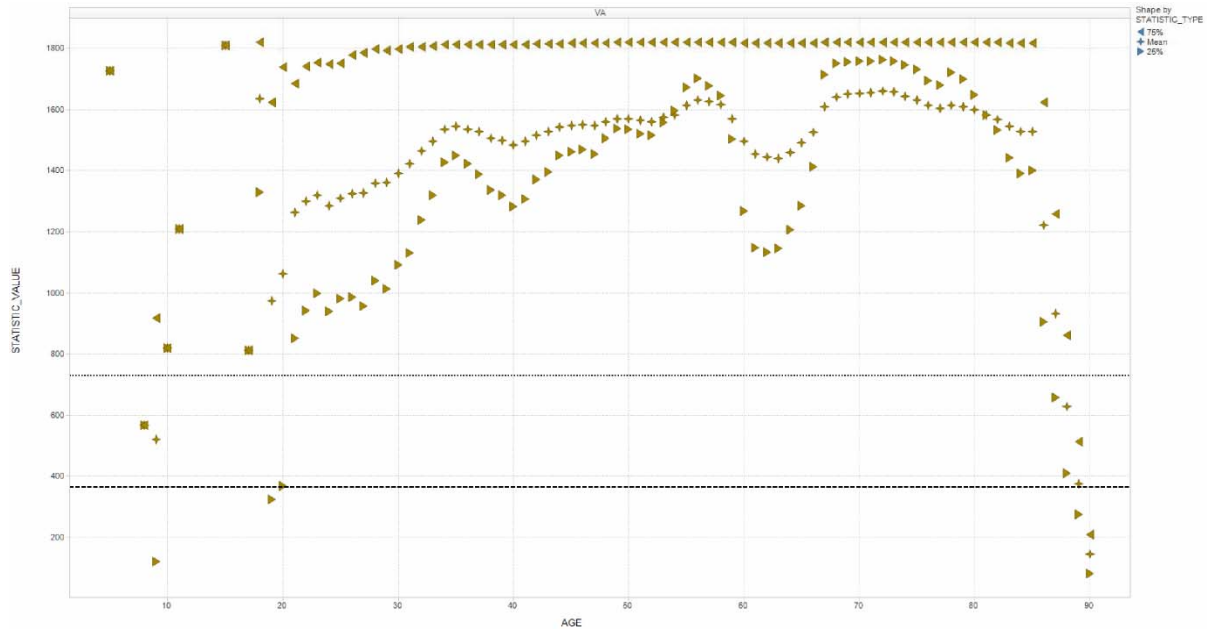


Table 2 shows counts for drug era and the number of persons as well as the mean age for males and females in the top 10 Drug of Interest (DOIs) for our CDM. Table 3 shows the number of occurrences for the top 10 Health Outcomes of Interest (HOIs) in our CDM. Note that:

- Our drug utilization pattern is different from the Community because we have a select cohort based on Statin prescriptions. Because of this, our patient cohort is most likely sicker and has a greater number of prescriptions.
- Our gender mix is very different from the Community as expected.
- Our population has higher condition occurrence counts, longer observational length for drugs, and a higher drug quantity due to their multiple co-morbidity conditions compared to the Community.

Table 2: Top 10 DOIs in VA Study Populations

DOI Name	Era Count	Person Count	Mean Age for Female	Mean Age for Male
ACE Inhibitor	5,620,998	1,914,533	64.0	70.3
Amphotericin B	66	43	56.7	66.1
Antibiotics	488,501	324,476	59.0	67.9
Antiepileptics	232,505	81,609	57.8	66.9
Benzodiazepines	2,004,207	631,482	57.8	66.9
Beta blockers	4,699,759	1,529,296	64.7	71.3
Bisphosphonates	320,344	119,912	71.2	76.2
Tricyclic Antidepressants	680,732	273,310	57.9	65.8
Typical antipsychotics	158,832	82,843	56.1	63.0
Warfarin	950,736	290,039	69.4	74.2

Table 3: Top 10 HOIs in VA Study Populations

HOI Name	Occurrence Count	Female Count	Mean Age for Female	Male Count	Mean Age for Male
Hospitalization #1	1,752,177	65,291	60.3	1,686,886	68.2
Bleeding #1	1,668,020	72,990	59.6	1,595,030	70.3
Bleeding #3	1,204,545	62,384	58.8	1,142,161	69.3
Acute Liver Failure #1	1,134,809	45,115	57.4	1,089,694	62.9
Acute Liver Failure #2	690,524	23,522	57.0	667,002	61.7
Acute myocardial Infarction #1	220,834	4,521	64.9	216,313	69.2
Bleeding #2	160,484	4,440	63.8	156,044	71.2
Acute Renal Failure #1	156,045	3,344	66.4	152,701	71.4
Acute Renal Failure #4	154,901	3,307	66.5	151,594	71.4
Acute myocardial Infarction #2	128,263	2,254	66.2	126,009	69.8

III. Performance Evaluation of Methods

1. Methods Implemented

Of the 13 methods released by OMOP, 11 ran successfully. The Bayesian Logistic Regression (BLR) method is still running. The IC Temporal Pattern Discovery method was not run due to issues with the R program. The table below shows the list of methods that were completed and the status of other methods that are not yet complete.

Table 4: Status of Method Implementation.

Analysis Method	Status of Run
Disproportionality analysis	Completed
Multi-set case control estimation	Completed
High-dimensional propensity score	Completed
Univariate self-controlled case series	Completed
Observational screening	Completed
maxSPRT	Completed
CSSP	Completed
Case-control surveillance	Completed
Case-crossover	Completed
HSIU cohort method	Completed
Incident User Design HOI method	Running the program still. We started late and this resource intensive program has been running slow on our system
Bayesian logistic regression	Not run - R Program has issue getting data from our SQL 2005 server. We did co-ordinate with partners and used the program that they used on their SQL server. We have been trying to troubleshoot some programming issues and to get help from OMOP R programmer. If the issues get resolved we intend to try the program.
hdPS- New user designs	Not released by OMOP

Statistical relational learning	Not released by OMOP
Multivariate self-controlled case series	Not released by OMOP

2. Performance Evaluations

The overall performance of the methods was evaluated using the area under receiver operating characteristic (ROC) curve (AUC). Specifically, our focus was on the AUC scores based on 1) all of the original 213 test cases (OVERALL), 2) only the test cases that are derived from health outcomes of interest (HOI) definitions that do not require laboratory values (NOLAB), and 3) all drug-outcome pairs that involve the first (diagnosis code only) definition of each HOI (BROAD).

Table 5 presents the summary statistics (mean, standard deviation, minimum, and maximum) of AUC scores for the VA and Community. As shown, the AUC scores calculated using all of the original 213 cases were relatively lower than the other AUCs regardless of the methods. In general, AUC scores based on the diagnosis only were slightly higher than AUC scores without using laboratory values (see Figure 8).

Table 5 also revealed that case-control surveillance (CCS), disproportionality (DP), high density propensity score (HDPS), observational screening (OS), and univariate self controlled case series (USCCS) methods perform better in terms of AUC than the other methods in analyzing the VA data. The conditional sequential sampling procedure (CSSP), incidence user design (IUD_HOI), and maximum sequential probability ratio test (maxSPRT) showed poor performances in our database. This is also shown graphically in Figure 9.

Comparison for AUC scores based on the diagnosis only between VA and Community can also be seen in Figure 9. The AUC scores varied for each method for each data source. However, it seems that CCS, DP, OS, and USCCS methods perform better for VA than Community.

The optimal AUC scores for VA and Community were compared in Figure 10. The AUC scores were very similar between the two sources for case crossover (CCO), CSSP, HDPS, high throughput safety-screening (HSIU), IUD_HOI, and multiset case control estimation (MSCCE). Figure 10 also shows that the performance for CCS, DP, OS, and USCCS methods were better for VA than Community. Note that maxSPRT performs better for Community than for VA.

Tables 6a – 6k present the summary statistics of AUC scores for different parameter settings within each method. In the USCCS method, setting the surveillance window to 30 days or 60 days following the end of exposure gives higher AUC scores compared to setting the surveillance window to 30 days from the initiation of exposure (see Table 6a). In the OS method, different parameter settings for drug exposure, outcome occurrence, or surveillance window didn't change the performance much. However, comparing the screening rates between post and pre showed better performance than comparing post and overall (Table 6b). The maxSPRT performed the worst in the VA data, possibly due to the fact that no adjustment was done (AUC ranges from 0.19 to 0.34 depending on the parameter settings). The incident user design (IUD_HOI) is one of the most poorly performing methods in the VA data (AUC ranges high 0.2 to low 0.4). It appears that when comparator 4 was used, it performed the best (Table 6e). In the HSIU, to count the condition with start date(s) within drug era or to count the condition with start date(s) after the start of drug didn't matter. Performance also did not change when stratification by sex was used (Table 6f). In the HDPS method, the method performs better when the covariates counted 30 days prior to exposure were used in the model and when outcomes occurred anytime after exposures were considered (Table 6g). In the DP method, use of the first occurrence, stratified by sex and age, and setting the surveillance window to 30 days performed better than any of the other settings. In addition, use of MGPS and the signed Chi-square as a disproportionality score counting provided better AUC scores (Table 6h). As mentioned, CSSP performed quite poorly (AUC ranges from low to mid 0.3) and the change of washout period (free of outcomes before index date) didn't change AUC scores significantly (Table 6i). The CCS method performed better when the minimum number of days between the index date of the event and the patients' start in the study was 90 days compared to 183 or 30 days (Table 6j). In the CCO method, the longer length of case and control windows performed better than the shorter window. It seems that in terms of the minimum number of days that individual must be observed before establishing doesn't matter in terms of affecting performance (Table 6k).

For reviewing the parameter settings for each method, the use of incident cases, following 30 days or 60 days from the end of exposure period, and stratifying by age or sex would be appropriate settings for the VA data. Further research is still needed to identify the most appropriate settings as well as to identify the most sensitive settings for the VA data. It seems that the methods that account for the case mix of the Veteran population would be the most appropriate given that the Veteran population is most likely to be older males with multiple co-morbidity conditions. VA databases are very comprehensive and changing VA databases would not improve the performance of the methods.

The precisions of each method for VA and Community are displayed in Figure 11. Precision ranges from 0 to 1 for most methods which makes it difficult to choose the better performing methods based on the precision. The optimal precisions (varying alpha and point estimate) for the both VA and Community are displayed in Figure 12. In terms of precision, most of the methods performed better when applied to the Community databases than the VA database.

The performance of the methods for each DOI and HOI pair has initially been explored using relative risk (RR). Some methods performed well for specific DOI and HOI pairs, but did not perform well for other pairs. Overall, methods that adjust for patient case mix performed well. We also observed that all RRs that were generated by IUD_HOI method were not statistically significant for all DOI and HOI pairs.

Although year one of the project has ended we continue to evaluate and assess the methods and outcomes. We currently meet once a week to assess the results for the DOIs and HOIs to determine why some of the methods are not working in our dataset and to further evaluate those methods to see if we can better explain the results. It is our intention to continue this process until we determine the best automated methods that fit our system.

Table 5: Comparison of AUCs between VA and Community Average

Method	Measure	VA					Community Average				
		n	Mean	STD	Min	Max	n	Mean	STD	Min	Max
CCO	AUC Overall	48	0.496	0.034	0.428	0.567	48	0.517	0.014	0.489	0.542
	AUC No Lab	48	0.576	0.040	0.494	0.654	48	0.565	0.016	0.537	0.597
	ACU Broad	48	0.559	0.056	0.452	0.639	48	0.595	0.016	0.570	0.620
CCS	AUC Overall	48	0.523	0.028	0.469	0.575	48	0.541	0.010	0.520	0.558
	AUC No Lab	48	0.597	0.036	0.525	0.665	48	0.566	0.010	0.544	0.586
	ACU Broad	48	0.631	0.065	0.508	0.710	48	0.572	0.014	0.539	0.604
CSSP	AUC Overall	18	0.302	0.022	0.274	0.343	18	0.313	0.034	0.275	0.367
	AUC No Lab	18	0.299	0.046	0.252	0.392	18	0.316	0.034	0.278	0.377
	ACU Broad	18	0.345	0.041	0.275	0.439	18	0.349	0.042	0.287	0.428
DP	AUC Overall	62	0.528	0.092	0.275	0.642	64	0.549	0.015	0.502	0.579
	AUC No Lab	62	0.614	0.100	0.343	0.758	64	0.590	0.020	0.532	0.632
	ACU Broad	62	0.610	0.087	0.379	0.722	64	0.609	0.020	0.557	0.645
HDPS	AUC Overall	120	0.483	0.056	0.378	0.569	120	0.522	0.049	0.372	0.579
	AUC No Lab	120	0.575	0.080	0.450	0.689	120	0.584	0.046	0.443	0.646
	ACU Broad	120	0.603	0.063	0.434	0.689	120	0.628	0.048	0.457	0.697
HSIU	AUC Overall	6	0.508	0.016	0.487	0.523	6	0.506	0.019	0.476	0.531
	AUC No Lab	6	0.542	0.024	0.510	0.566	6	0.524	0.025	0.490	0.554
	ACU Broad	6	0.547	0.014	0.530	0.563	6	0.533	0.020	0.504	0.554
IUD_HOI	AUC Overall	32	0.294	0.055	0.157	0.402	32	0.378	0.046	0.305	0.455
	AUC No Lab	32	0.368	0.066	0.199	0.503	32	0.411	0.053	0.320	0.494
	ACU Broad	32	0.373	0.063	0.298	0.487	32	0.381	0.060	0.288	0.466
MSCCE	AUC Overall	32	0.494	0.043	0.442	0.568	32	0.531	0.013	0.506	0.555
	AUC No Lab	32	0.569	0.047	0.513	0.652	32	0.569	0.010	0.553	0.591
	ACU Broad	32	0.568	0.049	0.500	0.667	32	0.590	0.012	0.572	0.619
MSPRT	AUC Overall	18	0.211	0.038	0.147	0.265	120	0.300	0.043	0.221	0.393
	AUC No Lab	18	0.245	0.036	0.180	0.299	120	0.319	0.054	0.198	0.433

	ACU Broad	18	0.316	0.042	0.250	0.402	120	0.340	0.072	0.235	0.543
OS	AUC Overall	54	0.541	0.033	0.463	0.607	54	0.516	0.022	0.440	0.554
	AUC No Lab	54	0.625	0.039	0.533	0.703	54	0.552	0.031	0.454	0.606
	ACU Broad	54	0.669	0.042	0.596	0.750	54	0.580	0.033	0.465	0.632
USCCS	AUC Overall	64	0.580	0.027	0.531	0.628	64	0.560	0.009	0.540	0.575
	AUC No Lab	64	0.683	0.043	0.604	0.753	64	0.614	0.011	0.591	0.639
	ACU Broad	64	0.725	0.042	0.646	0.775	64	0.639	0.015	0.612	0.666

Table 6a: Univariate Self Controlled Case Series

Parameter	Description	Measure	n	Mean	STD	Min	Max
Condition type	Prevalent (use consider all occurrences)	AUC Overall	32	0.573	0.029	0.531	0.617
		AUC with No Lab	32	0.671	0.045	0.604	0.733
		AUC Broad	32	0.716	0.041	0.646	0.770
	Incident (use first occurrence)	AUC Overall	32	0.588	0.023	0.556	0.628
		AUC with No Lab	32	0.696	0.038	0.637	0.753
		AUC Broad	32	0.733	0.041	0.649	0.775
Day from drug era start	0 day from the drug era start	AUC Overall	32	0.584	0.028	0.535	0.628
		AUC with No Lab	32	0.690	0.045	0.608	0.753
		AUC Broad	32	0.731	0.043	0.649	0.775
	1 day from the drug era start	AUC Overall	32	0.576	0.026	0.531	0.618
		AUC with No Lab	32	0.677	0.041	0.604	0.737
		AUC Broad	32	0.718	0.041	0.646	0.763
Surveillance window	Within 30 days of initiation of exposure	AUC Overall	16	0.549	0.013	0.531	0.563
		AUC with No Lab	16	0.629	0.019	0.604	0.652
		AUC Broad	16	0.660	0.010	0.646	0.674
	Anytime during the exposure	AUC Overall	16	0.566	0.010	0.551	0.582
		AUC with No Lab	16	0.664	0.017	0.639	0.688
		AUC Broad	16	0.726	0.023	0.689	0.755
	Anytime during or within 30 days following the end of exposure	AUC Overall	16	0.591	0.008	0.578	0.603
		AUC with No Lab	16	0.708	0.014	0.686	0.729
		AUC Broad	16	0.764	0.008	0.750	0.775
	Anytime during or within 60 days following the end of exposure	AUC Overall	16	0.615	0.008	0.599	0.628
		AUC with No Lab	16	0.732	0.013	0.707	0.753
		AUC Broad	16	0.747	0.011	0.732	0.765

Table 6b: Observation Screening

Parameter	Description	Measure	n	Mean	STD	Min	Max
Drug exposure	All exposure	AUC Overall	32	0.537	0.031	0.463	0.583
		AUC with No Lab	32	0.625	0.039	0.533	0.689
		AUC Broad	32	0.678	0.047	0.596	0.750
	First exposure	AUC Overall	22	0.547	0.036	0.472	0.607
		AUC with No Lab	22	0.625	0.041	0.548	0.703
		AUC Broad	22	0.656	0.029	0.611	0.705
Outcome occurrence	Prevalent (use consider all occurrences)	AUC Overall	26	0.542	0.029	0.482	0.583
		AUC with No Lab	26	0.630	0.034	0.564	0.689
		AUC Broad	26	0.678	0.044	0.606	0.750
	Incident (use first occurrence)	AUC Overall	14	0.541	0.033	0.482	0.587
		AUC with No Lab	14	0.623	0.039	0.564	0.679
		AUC Broad	14	0.667	0.036	0.631	0.730
Screening rate	POST/PRE	AUC Overall	38	0.555	0.023	0.509	0.607
		AUC with No Lab	38	0.643	0.028	0.598	0.703
		AUC Broad	38	0.686	0.037	0.611	0.750
	POST/Overall	AUC Overall	16	0.509	0.030	0.463	0.554
		AUC with No Lab	16	0.582	0.028	0.533	0.631
		AUC Broad	16	0.628	0.018	0.596	0.674
Counting of index date	Exclude the index date (date of initiation) in the PRE counts	AUC Overall	30	0.557	0.022	0.514	0.607
		AUC with No Lab	30	0.644	0.026	0.598	0.703
		AUC Broad	30	0.683	0.036	0.611	0.750
	Include the index date (date of initiation) in the PRE counts	AUC Overall	8	0.547	0.026	0.509	0.583
		AUC with No Lab	8	0.639	0.033	0.605	0.689
		AUC Broad	8	0.697	0.039	0.646	0.747

Surveillance window	30 days following the beginning of the drug era	AUC Overall	16	0.509	0.035	0.463	0.607
		AUC with No Lab	16	0.603	0.046	0.533	0.703
		AUC Broad	16	0.662	0.034	0.614	0.717
	-999	AUC Overall	4	0.542	0.028	0.517	0.571
		AUC with No Lab	4	0.598	0.031	0.572	0.632
		AUC Broad	4	0.624	0.013	0.611	0.636
	The length of the drug era plus 30 days	AUC Overall	34	0.556	0.019	0.515	0.590
		AUC with No Lab	34	0.638	0.030	0.574	0.689
		AUC Broad	34	0.677	0.044	0.596	0.750

Table 6c: Maximized Sequential probability Ratio Test

Parameter	Description	Measure	n	Mean	STD	Min	Max
Washout Window	Period free of outcomes before index date - 183	AUC Overall	6	0.223	0.038	0.172	0.265
		AUC with No Lab	6	0.259	0.035	0.211	0.297
		AUC Broad	6	0.342	0.021	0.306	0.366
	Period free of outcomes before index date - 400	AUC Overall	6	0.212	0.041	0.150	0.262
		AUC with No Lab	6	0.247	0.041	0.185	0.299
		AUC Broad	6	0.317	0.052	0.255	0.402
	Period free of outcomes before index date - 91	AUC Overall	6	0.198	0.036	0.147	0.243
		AUC with No Lab	6	0.230	0.032	0.180	0.261
		AUC Broad	6	0.290	0.035	0.250	0.341
Significance Level	0.001	AUC Overall	9	0.194	0.038	0.147	0.263
		AUC with No Lab	9	0.228	0.037	0.180	0.297
		AUC Broad	9	0.295	0.039	0.250	0.354
	0.05	AUC Overall	9	0.228	0.030	0.185	0.265
		AUC with No Lab	9	0.262	0.027	0.223	0.299
		AUC Broad	9	0.338	0.033	0.293	0.402

Table 6d: Multi-set case-control estimation

Parameter	Description	Measure	n	Mean	STD	Min	Max
Number of matches	10	AUC Overall	10	0.470	0.025	0.442	0.506
		AUC with No Lab	10	0.538	0.022	0.513	0.573
		AUC Broad	10	0.536	0.015	0.520	0.571
	1000	AUC Overall	1000	0.519	0.045	0.442	0.568
		AUC with No Lab	1000	0.599	0.045	0.514	0.652
		AUC Broad	1000	0.599	0.050	0.500	0.670
Days Enrolled	183	AUC Overall	8	0.487	0.043	0.448	0.556
		AUC with No Lab	8	0.559	0.047	0.525	0.634
		AUC Broad	8	0.546	0.048	0.500	0.626
	30	AUC Overall	8	0.505	0.039	0.454	0.558
		AUC with No Lab	8	0.582	0.040	0.531	0.636
		AUC Broad	8	0.580	0.042	0.525	0.626
	400	AUC Overall	8	0.484	0.054	0.442	0.568
		AUC with No Lab	8	0.556	0.059	0.513	0.652
		AUC Broad	8	0.571	0.058	0.520	0.667
	91	AUC Overall	8	0.501	0.040	0.445	0.552
		AUC with No Lab	8	0.577	0.042	0.518	0.630
		AUC Broad	8	0.575	0.047	0.520	0.624
Risk window	30 days	AUC Overall	16	0.464	0.025	0.442	0.506
		AUC with No Lab	16	0.542	0.031	0.513	0.594
		AUC Broad	16	0.551	0.043	0.500	0.626
	60 days	AUC Overall	16	0.525	0.036	0.472	0.568
		AUC with No Lab	16	0.595	0.045	0.527	0.652
		AUC Broad	16	0.584	0.049	0.520	0.667

Table 6e: Incident user design

Parameter	Description	Measure	n	Mean	STD	Min	Max
ITT	No	AUC Overall	16	0.275	0.053	0.157	0.377
		AUC with No Lab	16	0.346	0.064	0.199	0.470
		AUC Broad	16	0.355	0.052	0.298	0.449
	Yes	AUC Overall	16	0.312	0.052	0.248	0.402
		AUC with No Lab	16	0.391	0.063	0.311	0.503
		AUC Broad	16	0.391	0.069	0.306	0.487
PS	HDPS	AUC Overall	16	0.314	0.054	0.243	0.402
		AUC with No Lab	16	0.391	0.064	0.310	0.503
		AUC Broad	16	0.393	0.061	0.298	0.477
	PS	AUC Overall	16	0.274	0.050	0.157	0.359
		AUC with No Lab	16	0.346	0.062	0.199	0.451
		AUC Broad	16	0.353	0.060	0.298	0.487
TRIM	No	AUC Overall	16	0.290	0.062	0.157	0.402
		AUC with No Lab	16	0.364	0.075	0.199	0.503
		AUC Broad	16	0.375	0.065	0.298	0.487
	Yes	AUC Overall	16	0.297	0.049	0.243	0.379
		AUC with No Lab	16	0.373	0.059	0.310	0.476
		AUC Broad	16	0.371	0.062	0.298	0.480
Comparator group	Group 1	AUC Overall	8	0.258	0.025	0.243	0.315
		AUC with No Lab	8	0.331	0.030	0.310	0.400
		AUC Broad	8	0.319	0.028	0.298	0.386
	Group 2	AUC Overall	8	0.297	0.032	0.253	0.335
		AUC with No Lab	8	0.367	0.034	0.317	0.404
		AUC Broad	8	0.384	0.021	0.359	0.407
	Group 3	AUC Overall	8	0.267	0.059	0.157	0.344
		AUC with No Lab	8	0.334	0.072	0.199	0.428
		AUC Broad	8	0.363	0.075	0.298	0.477
	Group 4	AUC Overall	8	0.352	0.044	0.263	0.402
		AUC with No Lab	8	0.442	0.054	0.333	0.503
		AUC Broad	8	0.425	0.063	0.298	0.487

Table 6f: HSIU cohort method

Parameter	Description	Measure	n	Mean	STD	Min	Max
Counting of condition	Count condition after the start of drug	AUC Overall	3	0.521	0.001	0.520	0.523
		AUC with No Lab	3	0.562	0.003	0.560	0.566
		AUC Broad	3	0.546	0.016	0.530	0.563
	Count condition within the start of drug	AUC Overall	3	0.494	0.008	0.487	0.503
		AUC with No Lab	3	0.521	0.012	0.510	0.535
		AUC Broad	3	0.547	0.014	0.535	0.563
Stratification by sex	No	AUC Overall	2	0.504	0.024	0.487	0.521
		AUC with No Lab	2	0.535	0.035	0.510	0.560
		AUC Broad	2	0.540	0.007	0.535	0.545
	Yes	AUC Overall	4	0.510	0.014	0.493	0.523
		AUC with No Lab	4	0.545	0.022	0.519	0.566
		AUC Broad	4	0.550	0.016	0.530	0.563

Table 6g: High-dimensional Propensity Score

Parameter	Description	Measure	n	Mean	STD	Min	Max
Covariate eligibility	180 days prior to exposure	AUC Overall	60	0.480	0.057	0.378	0.569
		AUC with No Lab	60	0.571	0.081	0.463	0.689
		AUC Broad	60	0.592	0.062	0.434	0.684
	30 days B7prior to exposure	AUC Overall	30	0.490	0.054	0.400	0.563
		AUC with No Lab	30	0.582	0.080	0.450	0.684
		AUC Broad	30	0.627	0.053	0.500	0.684
	Anytime prior to exposure	AUC Overall	30	0.484	0.057	0.390	0.566
		AUC with No Lab	30	0.577	0.080	0.459	0.683
		AUC Broad	30	0.601	0.069	0.462	0.689
Surveillance window	- 30 days	AUC Overall	40	0.483	0.048	0.378	0.541
		AUC with No Lab	40	0.585	0.064	0.468	0.667
		AUC Broad	40	0.590	0.080	0.434	0.689
	anytime after	AUC Overall	40	0.491	0.063	0.419	0.569
		AUC with No Lab	40	0.581	0.089	0.479	0.689
		AUC Broad	40	0.633	0.050	0.508	0.684
	+ 30 days	AUC Overall	40	0.475	0.058	0.400	0.549
		AUC with No Lab	40	0.560	0.084	0.450	0.664
		AUC Broad	40	0.585	0.043	0.495	0.659
Top counters	Maximal number of covariates = 100	AUC Overall	90	0.485	0.056	0.390	0.569
		AUC with No Lab	90	0.578	0.079	0.450	0.689
		AUC Broad	90	0.608	0.063	0.434	0.689
	maximum number of covariates = 500	AUC Overall	30	0.476	0.058	0.378	0.563
		AUC with No Lab	30	0.567	0.081	0.463	0.684
		AUC Broad	30	0.588	0.061	0.495	0.684

Table 6h: Disproportionality Analysis

Parameter	Description	Measure	n	Mean	STD	Min	Max
Condition type	Prevalent (use consider all occurrences)	AUC Overall	30	0.484	0.110	0.275	0.620
		AUC with No Lab	30	0.563	0.116	0.343	0.722
		AUC Broad	30	0.557	0.096	0.379	0.692
	Incident (use first occurrence)	AUC Overall	32	0.570	0.040	0.512	0.642
		AUC with No Lab	32	0.662	0.048	0.583	0.758
		AUC Broad	32	0.661	0.026	0.621	0.722
DP score counting	Proportional reporting ratio	AUC Overall	16	0.515	0.100	0.275	0.616
		AUC with No Lab	16	0.599	0.108	0.343	0.720
		AUC Broad	16	0.598	0.094	0.379	0.697
	BCPNN	AUC Overall	16	0.515	0.100	0.275	0.616
		AUC with No Lab	16	0.599	0.108	0.343	0.720
		AUC Broad	16	0.597	0.093	0.379	0.697
	MGPS	AUC Overall	14	0.551	0.045	0.492	0.628
		AUC with No Lab	14	0.636	0.055	0.568	0.734
		AUC Broad	14	0.626	0.042	0.545	0.697
	Signed Chi-square	AUC Overall	16	0.535	0.107	0.279	0.642
		AUC with No Lab	16	0.625	0.117	0.350	0.758
		AUC Broad	16	0.622	0.103	0.379	0.722
Stratified by age	No	AUC Overall	31	0.511	0.082	0.276	0.582
		AUC with No Lab	31	0.587	0.083	0.345	0.661
		AUC Broad	31	0.595	0.078	0.379	0.659
	Yes	AUC Overall	31	0.545	0.099	0.275	0.642
		AUC with No Lab	31	0.641	0.109	0.343	0.758
		AUC Broad	31	0.626	0.093	0.379	0.722
Stratified by sex	No	AUC Overall	31	0.511	0.082	0.276	0.582
		AUC with No Lab	31	0.587	0.083	0.345	0.661
		AUC Broad	31	0.595	0.078	0.379	0.659
	Yes	AUC Overall	31	0.545	0.099	0.275	0.642

		AUC with No Lab	31	0.641	0.109	0.343	0.758
		AUC Broad	31	0.626	0.093	0.379	0.722
Surveillance window	Within 30 days of initiation of exposure	AUC Overall	16	0.510	0.014	0.492	0.547
		AUC with No Lab	16	0.603	0.025	0.568	0.664
		AUC Broad	16	0.640	0.036	0.591	0.722
	Anytime during or within 30 days following the end of exposure	AUC Overall	16	0.581	0.028	0.544	0.638
		AUC with No Lab	16	0.667	0.042	0.613	0.754
		AUC Broad	16	0.638	0.030	0.601	0.705
	Anytime during or within 60 days following the end of exposure	AUC Overall	16	0.564	0.043	0.505	0.642
		AUC with No Lab	16	0.648	0.058	0.574	0.758
		AUC Broad	16	0.608	0.053	0.545	0.710
	Anytime after exposure	AUC Overall	14	0.448	0.155	0.275	0.624
		AUC with No Lab	14	0.527	0.165	0.343	0.726
		AUC Broad	14	0.547	0.152	0.379	0.697

Table 6i: Conditional Sequential Sampling Procedure

Parameter	Description	Measure	n	Mean	STD	Min	Max
Washout window	183 days before index date	AUC Overall	6	0.306	0.023	0.281	0.343
		AUC with No Lab	6	0.305	0.047	0.265	0.392
		AUC Broad	6	0.364	0.041	0.328	0.439
	400 days before index date	AUC Overall	6	0.298	0.022	0.275	0.335
		AUC with No Lab	6	0.345	0.050	0.252	0.387
		AUC Broad	6	0.345	0.019	0.326	0.379
	91 days before index date	AUC Overall	6	0.301	0.025	0.274	0.340
		AUC with No Lab	6	0.297	0.048	0.253	0.366
		AUC Broad	6	0.327	0.055	0.275	0.424
Significance level	0.001	AUC Overall	9	0.300	0.027	0.274	0.343
		AUC with No Lab	9	0.298	0.060	0.252	0.392
		AUC Broad	9	0.348	0.051	0.275	0.439
	0.05	AUC Overall	9	0.307	0.014	0.294	0.340
		AUC with No Lab	9	0.300	0.028	0.279	0.366
		AUC Broad	9	0.343	0.031	0.326	0.424

Table 6j: Case-Control Surveillance

Parameter	Description	Measure	n	Mean	STD	Min	Max
Lead time	minimum of 183 days between Dx date and start date	AUC Overall	16	0.520	0.027	0.473	0.567
		AUC with No Lab	16	0.592	0.036	0.528	0.654
		AUC Broad	16	0.633	0.068	0.518	0.702
	minimum of 30 days between Dx date and start date	AUC Overall	16	0.519	0.029	0.483	0.575
		AUC with No Lab	16	0.592	0.038	0.547	0.665
		AUC Broad	16	0.604	0.067	0.508	0.710
	minimum of 90 days between Dx date and start date	AUC Overall	16	0.530	0.027	0.469	0.570
		AUC with No Lab	16	0.607	0.036	0.525	0.660
		AUC Broad	16	0.656	0.054	0.528	0.702

Table 6k: Case Crossover

Parameter	Description	Measure	n	Mean	STD	Min	Max
Minimum observed period	Criteria for establishing incident COI - 180	AUC Overall	24	0.495	0.035	0.428	0.567
		AUC with No Lab	24	0.574	0.041	0.494	0.654
		AUC Broad	24	0.558	0.578	0.452	0.634
	Criteria for establishing incident COI - 91	AUC Overall	24	0.496	0.033	0.428	0.563
		AUC with No Lab	24	0.576	0.039	0.497	0.649
		AUC Broad	24	0.561	0.056	0.457	0.639
Length of case window	180 days	AUC Overall	8	0.528	0.040	0.466	0.567
		AUC with No Lab	8	0.603	0.049	0.530	0.654
		AUC Broad	8	0.588	0.049	0.513	0.631
	30 days	AUC Overall	24	0.480	0.026	0.428	0.507
		AUC with No Lab	24	0.570	0.035	0.501	0.609
		AUC Broad	24	0.546	0.055	0.452	0.606
	90 days	AUC Overall	16	0.504	0.027	0.448	0.545
		AUC with No Lab	16	0.570	0.038	0.494	0.620
		AUC Broad	16	0.565	0.057	0.487	0.639
Length of control window	180 days	AUC Overall	24	0.511	0.032	0.452	0.567
		AUC with No Lab	24	0.591	0.034	0.530	0.654
		AUC Broad	24	0.577	0.046	0.495	0.631
	30 days	AUC Overall	8	0.456	0.026	0.428	0.492
		AUC with No Lab	8	0.536	0.033	0.501	0.596
		AUC Broad	8	0.486	0.040	0.452	0.553
	90 days	AUC Overall	16	0.493	0.020	0.448	0.522
		AUC with No Lab	16	0.572	0.036	0.494	0.609
		AUC Broad	16	0.569	0.048	0.487	0.639

Figure 8

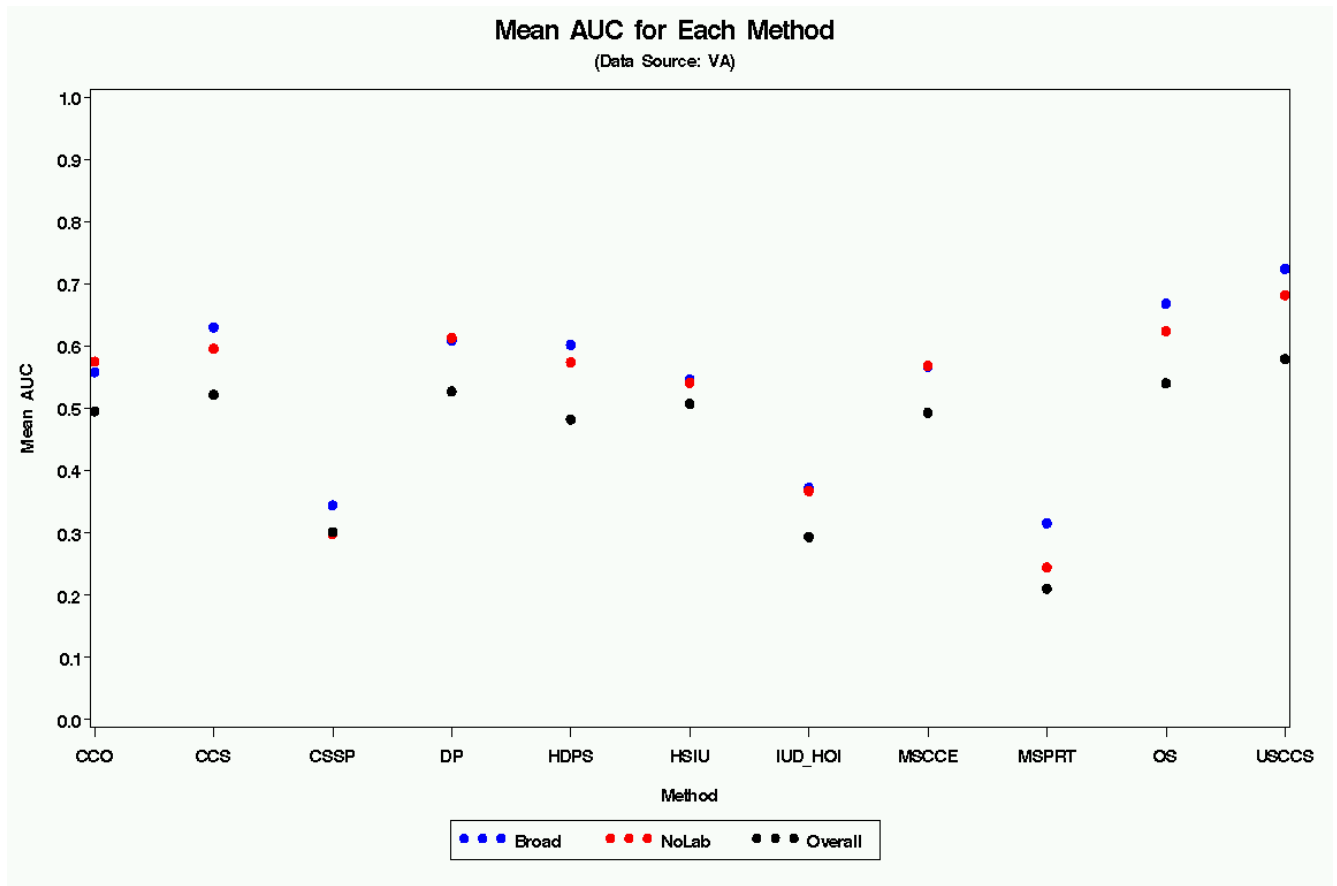


Figure 9

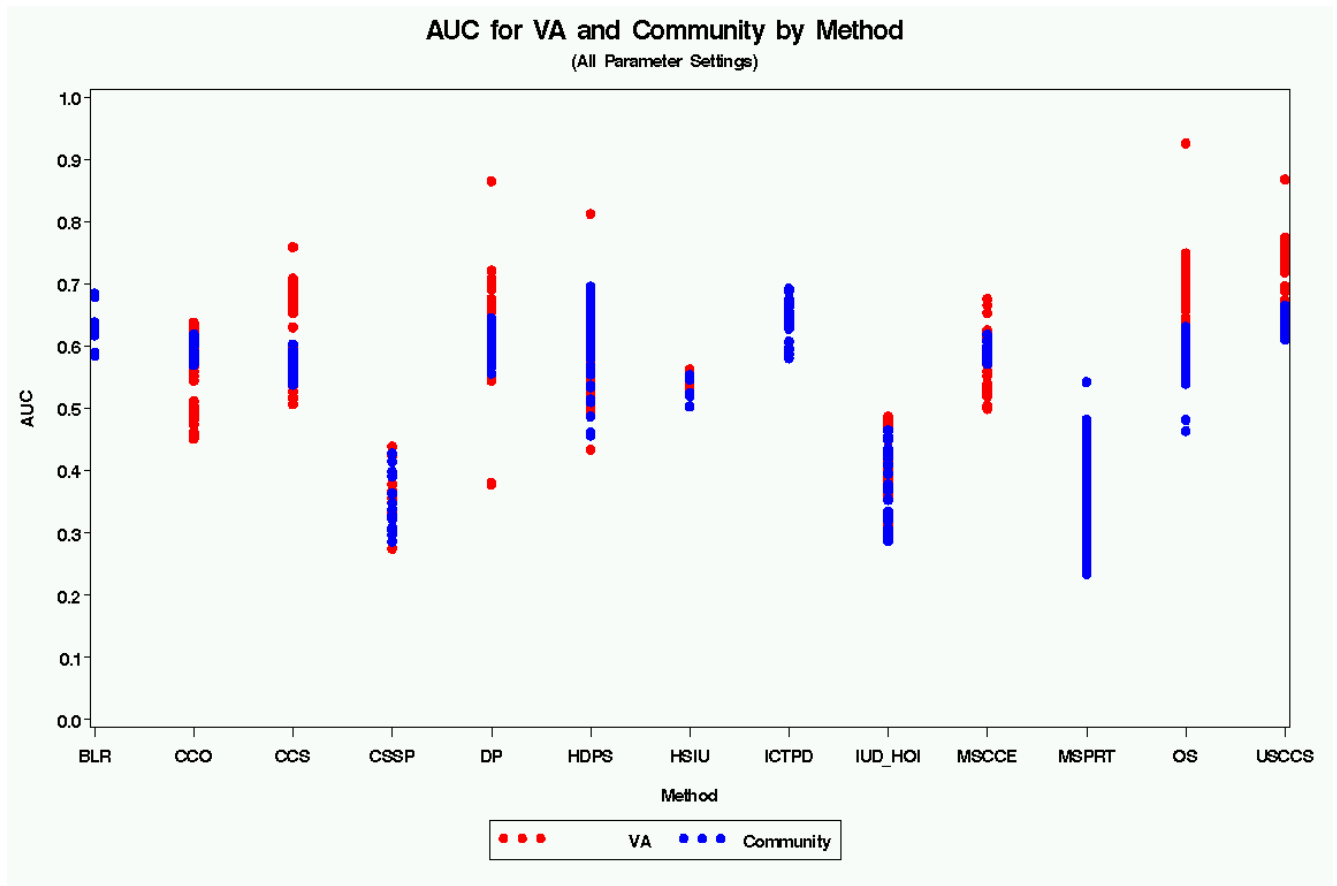


Figure 10

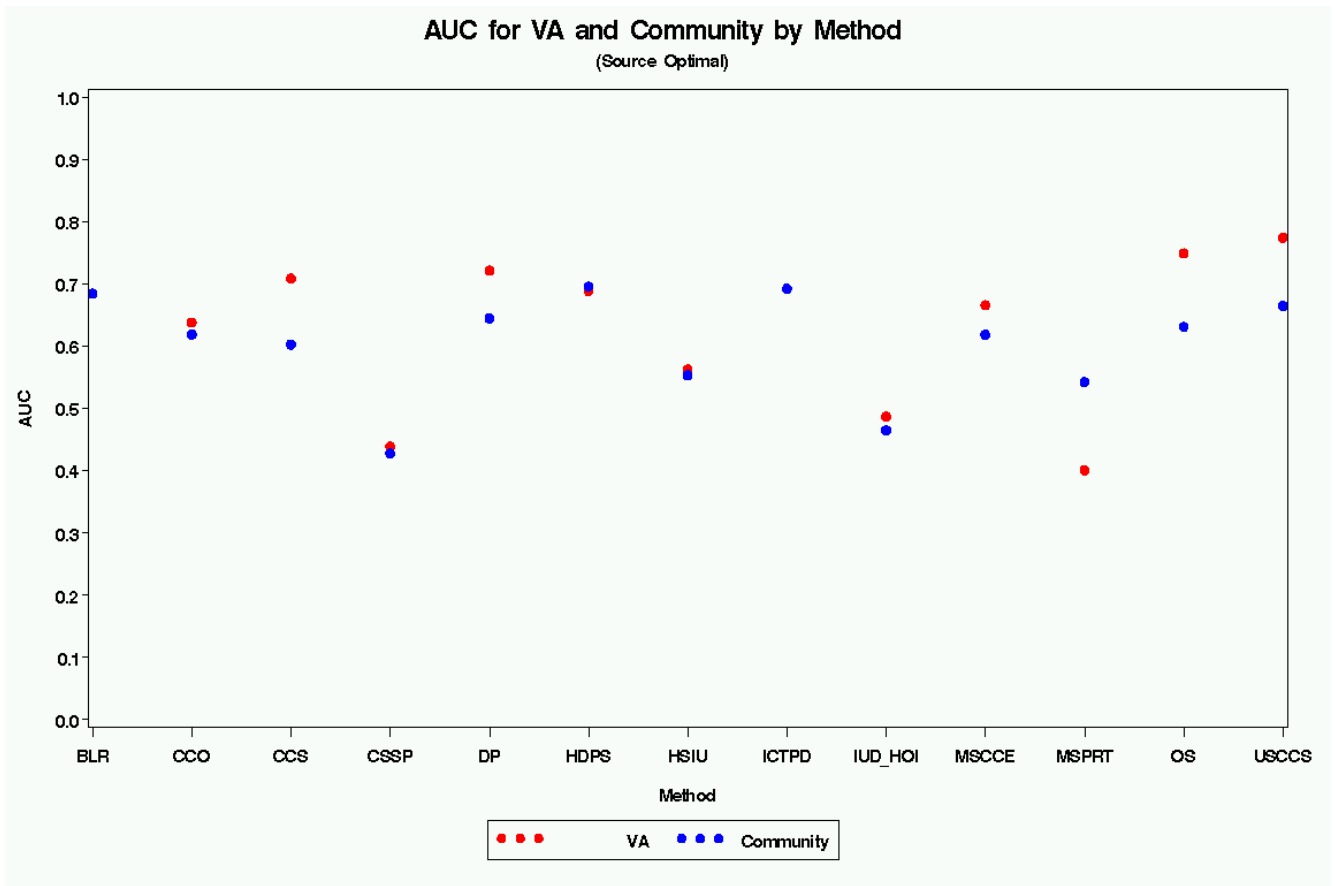
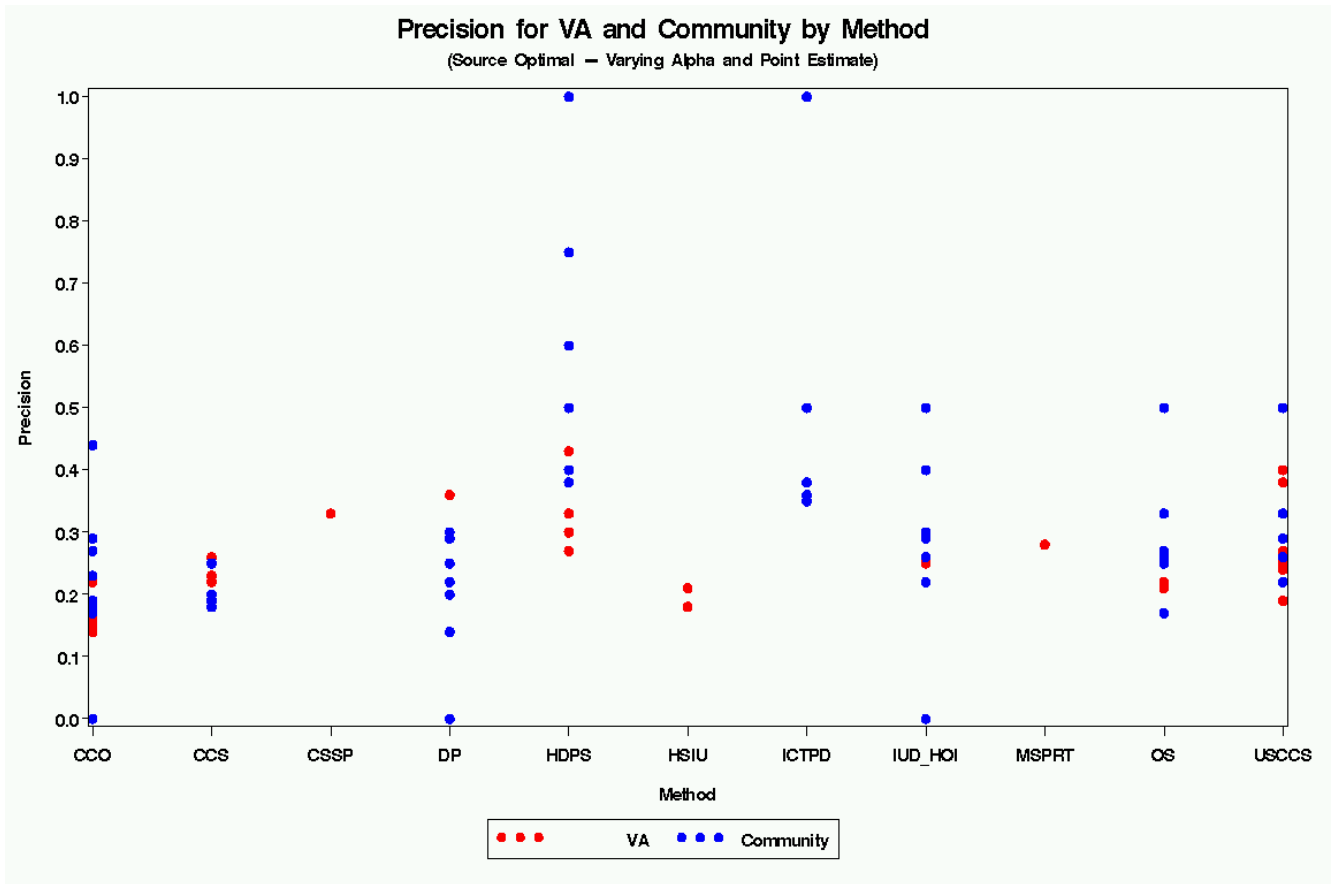


Figure 12



IV. Lessons Learned

1. Lessons Learned

The OMOP project has been an excellent experience and we learned some very valuable lessons. One of the important lessons was to continue to run a frequency on data both prior to and after transfer for count validation. With a dataset this large it is paramount to do both continually. Due to the data size we were unable to follow our standardized data transfer methodologies. We learned that any deviation from standard protocol for expediting a transfer is not optimal. Also, utilization of multiple software for data transfers can result in formatting issues and may cause data to be lost, as shown by the fact that we later discovered that we had 3 months worth of drug data missing.

Knowing what we know now we would have run our CDM and methodologies a bit differently. Some of things that we would have done differently are:

- Converted the CDM data into SQL tables as well. This may have helped us run methods like ICTPD. However, due to space constraints that may not have been possible. This is something that we are planning to do in the immediate future.
- Run general VA population characteristics versus U.S. population characteristics (i.e. Table 1) that could be used to plot graphs along with the CDM outputs to better understand the difference in distribution for our patient population.
- Assured the delivery of a server prior to initiating the project but due to time constraints and VA rules for obtaining IT tools this was beyond our control. In the future we will assure server access either by using what is available or borrowing space for such a sizeable analysis.
- Developed a program to conduct evaluations similar to GROUCH on our data.

We have successfully developed the CDM for the OMOP project by combining data elements from various databases in the VA system. We are confident that we can map our data in the future if we were to develop a new CDM.

Suggestions for OMOP

Listed below are a few recommendations for OMOP to consider.

- There are a plethora of things that each program/methods would touch upon. This often created space or system related issues. Therefore, if there was a synopsis available of what each program could do and a

summary of the tables that would be involved, it would allow for better assessment and control of resource planning.

- Also, an estimated time of completion based on records would be a great improvement in managing the order of submission of OMOP methods. This would better help plan and manage system and programmers' time for optimal efficiency.
- Given the sheer number of runs for each method, it would be beneficial to provide or request that the investigator create an efficient tracking tool for completions for each run. This tool could also account for tests done by OMOP and status updates on output transfers to OMOP. This could be a shared tracking tool to keep everyone involved on the same page.

2. Comments

We believe that a significant amount of research is needed to fully understand these results. The performance of the methods varies depending on the parameter settings (i.e., prevalence or incidence, length of risk window or surveillance window, etc). Thus, additional sensitivity analyses would be needed to examine the effects of change in a specific parameter. For example, the performance of each method can be evaluated by fixing one of the parameters and varying other parameters. This would allow us to see which specific parameters make significant changes in the performance.

It seems that many of the methods we have evaluated are better suited for signal strengthening/refinement and not for signal detection. Nevertheless, VA will continue to evaluate these results and based on our initial evaluation of the performances, more attention will be given to the DP, HDPS, OS, and USCCS methods.

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