Afternoon Session A:
Applications in Medical Product Safety

CIDA Report Interpretation

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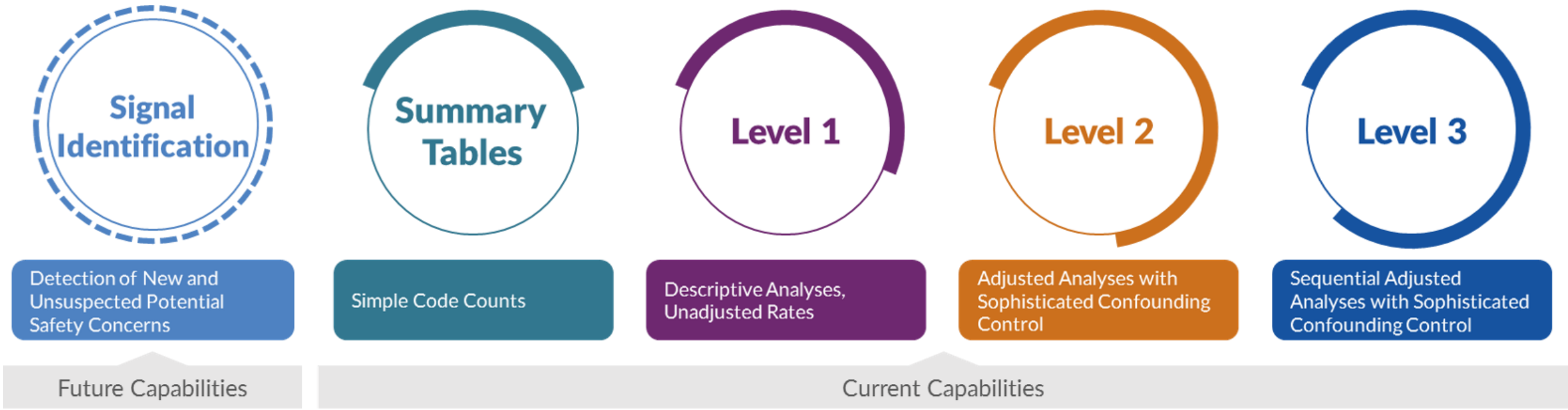
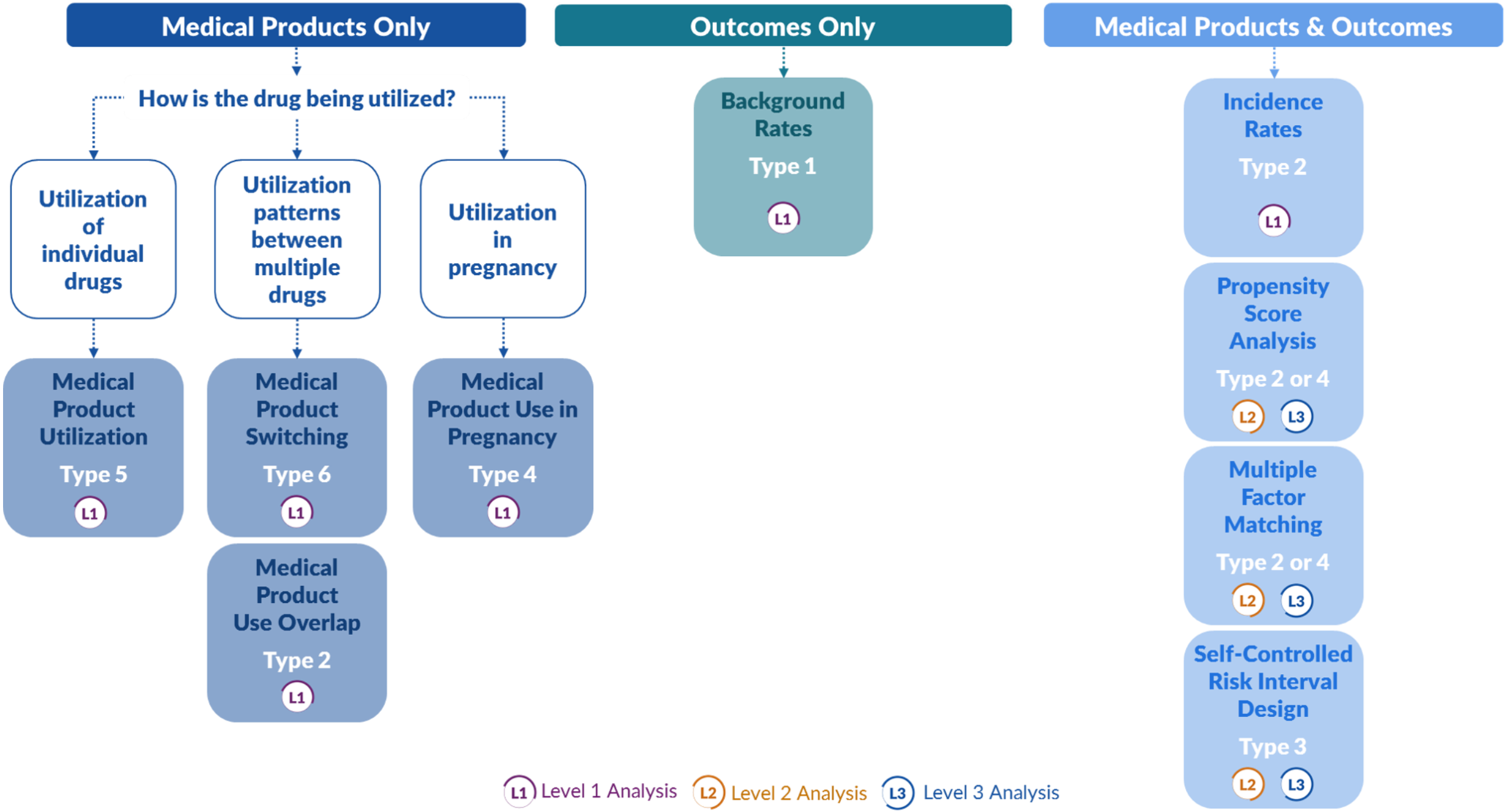
Active Risk Identification and Analysis (ARIA)



- Template computer programs with standardized questions
- Parameterized at program execution
- Pre-tested and quality-checked
- Standard output

https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria

What are you investigating?

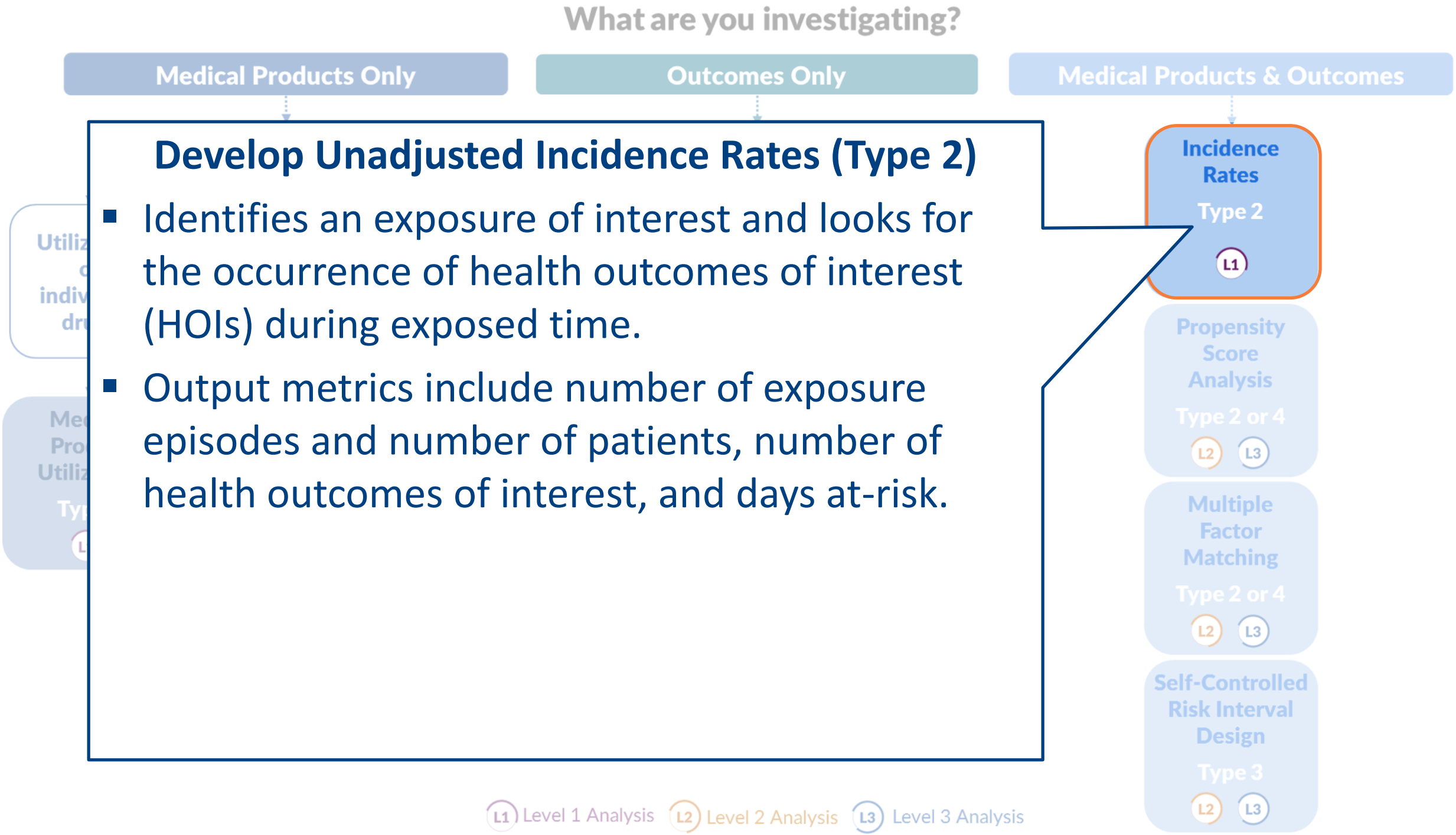


Agenda

- Review of Query Design
- Interpretation of Report Contents

Topics

- Baseline Characteristics
- Type 2 Report
- Propensity Score Analysis


What are you investigating?
Medical Products Only
Outcomes Only
Medical Products & Outcomes
Develop Unadjusted Incidence Rates (Type 2)
Identifies an exposure of interest and looks for the occurrence of health outcomes of interest (HOIs) during exposed time.
Output metrics include number of exposure episodes and number of health outcomes of interest, and days at-risk.
Incidence Rates
Type 2
L1
Propensity Score Analysis
Type 2 or 4
L2
L3
Multiple Factor Matching
Type 2 or 4
L2
L3
Self-Controlled Risk Interval Design
Type 3
L2
L3
L1 Level 1 Analysis
L2 Level 2 Analysis
L3 Level 3 Analysis

Recap of this Morning's Session

- Introduced our case study problem
  - Stroke following antipsychotics use
- Evaluated medical product utilization data
  - Sentinel Query Builder (Simplified Type 5 CIDA) Analysis Tool
- Introduced design diagram and query specifications for an incidence rates query with associated propensity score matching analysis
  - How to parameterize the regulatory question

Query Design

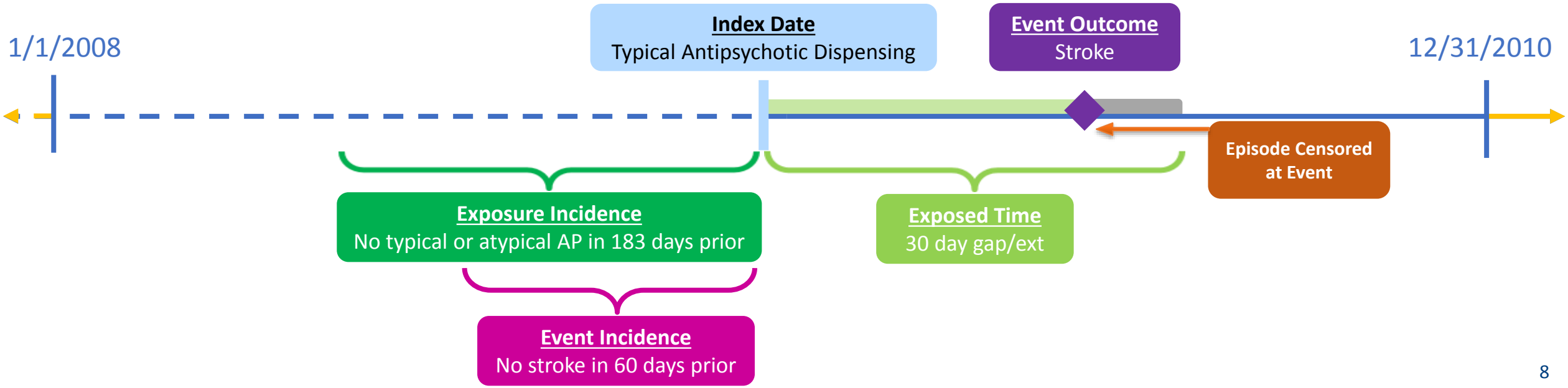
Covariate Evaluation Window
183 days to 1 day prior to index

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



Baseline Output

- Default output table characterizes each exposure/outcome scenario for:
  - Age
  - Sex
  - Race
  - Year of exposure
  - User-defined conditions
  - Medical and drug utilization metrics
  - Comorbidity score
- Evaluation for conditions occurs in flexible periods of time relative to the index date

Baseline Table

User specified age categories

Sex

Year

Covariates

Table 1a. Baseline table for Typical Antipsychotics		
	Typical Antipsychotics	
Characteristic[1]	N/Mean	%/Std Dev[2]
Number of episodes	24,720	
Number of unique patients	24,720	
Demographics		
Mean Age	51.6	10.6
Age: 18-39	4,186	16.9%
Age: 40-54	9,585	38.8%
Age: 55-65	10,949	44.3%
Gender (Female)	13,177	53.3%
Gender (Male)	11,543	46.7%
Year (2008)	7,318	29.6%
Year (2009)	11,669	47.2%
Year (2010)	5,733	23.2%
Recorded history of:		
AMI	3,335	13.5%
Diabetes	14,444	58.4%
Heart failure	7,207	29.2%
Hypercholesterolemia	13,612	55.1%
Hypertension	17,000	68.8%
Kidney failure	7,491	30.3%
Depression	7,537	30.5%
Anxiety	4,006	16.2%
Bipolar	6,708	27.1%
Schizophrenia/psychotic	5,834	23.6%
Substance abuse	2,348	9.5%
Transient ischemic attack	991	4.0%

- Table 1s show baseline characteristics
- Baseline table created for each exposure/outcome scenario (Tables 1a – 1d)

Type 2 Report - Overall Summary Counts

Table 2. Summary of Typical and Atypical Antipsychotics and Stroke in the Sentinel Distributed Database between January 1, 2008 and December 31, 2010 Overall

	New Users	Eligible Members[1]	New Episodes	Days At Risk	Years at Risk	Adjusted Dispensings	Raw Dispensings	Days Supplied	Amount Supplied	New Episodes with an Event	Eligible Member-Days[1]	Eligible Member Years[1]
Ischemic Stroke												
Typical Antipsychotics	24,720	275,462	24,720	1,466,593	4,015.3	25,963	25,964	780,011	1,215,820	19	138,151,408	378,237.9
Atypical Antipsychotics	19,470	275,462	19,470	1,149,639	3,147.5	19,977	19,979	616,789	1,019,508	10	139,376,883	381,593.1
Intracranial Hemorrhage												
Typical Antipsychotics	24,004	275,322	24,004	1,425,097	3,901.7	25,215	25,216	757,906	1,181,054	3	135,311,139	370,461.7
Atypical Antipsychotics	18,919	275,322	18,919	1,117,446	3,059.4	19,412	19,414	599,796	992,025	1	136,453,261	373,588.7

[1]Eligible Members, Member-Days, and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period

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Who are Eligible Members?

- Eligible Members, Member-Days, and Member-Years
  - Reflective of the number of members that met all cohort entry criteria on at least one day during the query period (*i.e., those eligible for an index event)*
  - Restricted to health plan members at participating Data Partners and may not be nationally representative
- In this query:
  - 18-65 years
  - Medical and drug coverage for 183 days
  - No exposure in -183 days (washout for exposure)
  - No stroke in -60 days (washout for outcome)
  - No dementia in -183 days (exclusion)

Who are Eligible Members? continued

Lymphoma HOI* validation project, CIDA workplan to id cases chart review

- Algorithm to validate: 2 lymphoma dx codes within 183 days, first is index and incident, have biopsy and imaging px codes within +/- 90 days of index

→ Eligible Members:

- ≥15 years
- Medical and drug coverage for 365 days
- No lymphoma is -183 days (washout for cohort)
- Biopsy px code in +/- 90 days
- Imaging px code in +/- 90 days

*Health outcome of interest

CIDA Denominators – for Types 1 and 2

- Eligible members
  - Number of members eligible for an index date
  - Must meet enrollment requirements, washout criteria, and inclusion/exclusion criteria for at least one day during the query period
- Eligible member days
  - All the days during the query period that an eligible member is eligible for inclusion in the cohort

- Tool assesses members every day of query period and counts eligible member days
- If you have at least 1 eligible day, you are an eligible member

Type 2 Report - Overall Summary Counts

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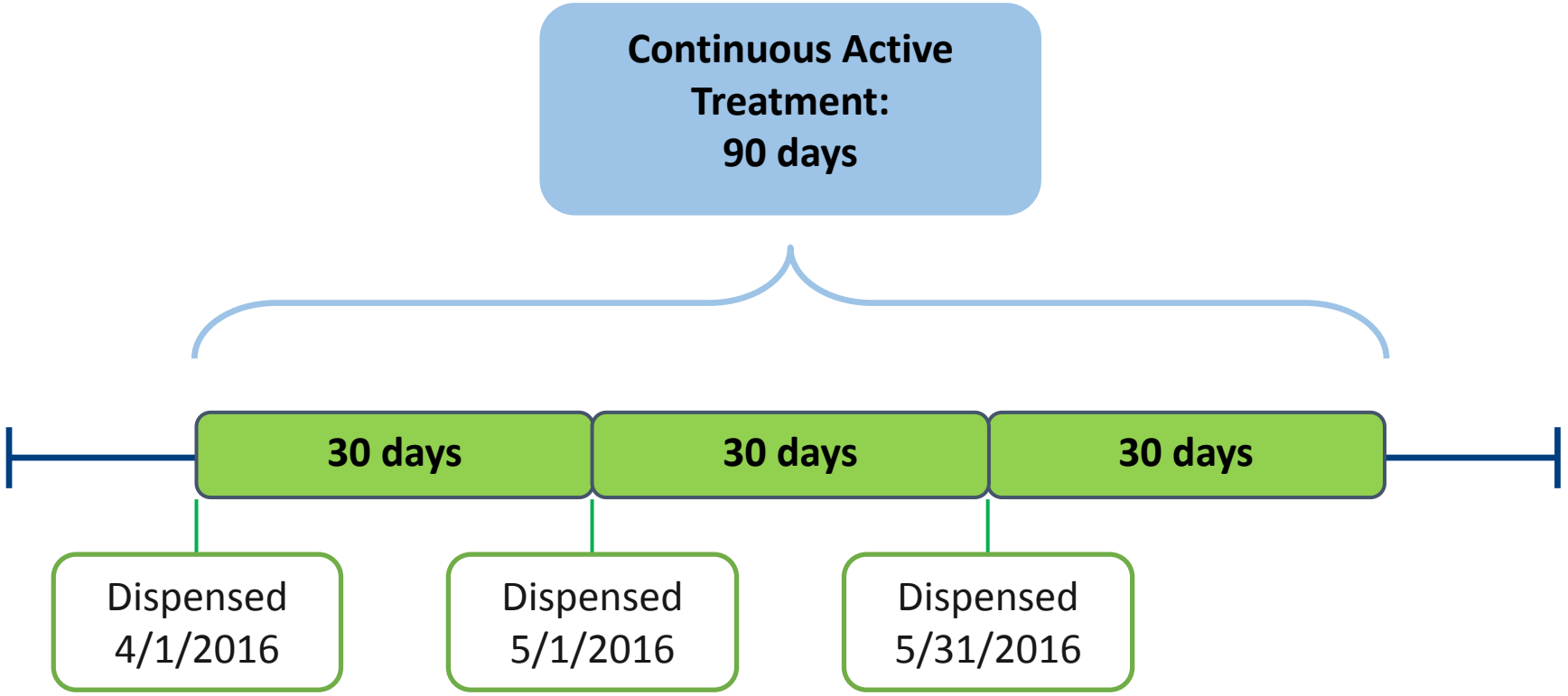
Adjusted vs Raw Code Counts

 # Patients: 1
 # Episodes: 1
Adjusted Code Count: 3
Raw Code Count: 3



Adjusted vs Raw Code Counts

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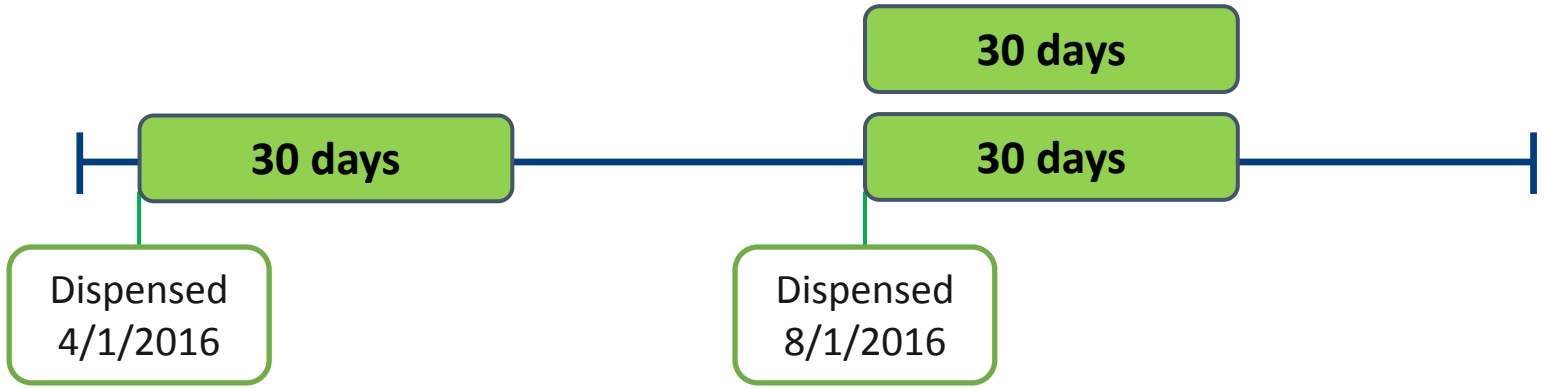

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Stratification of Results

- The CIDA tool can stratify select results from all cohort identification strategies by age, sex, year, month, race, and certain geographic information.
- Stratifications are user-defined.
- Custom strata may be defined in the CIDA tool from lists of valid stratification variables specific to each method of cohort identification.
- Results may also be stratified by defined covariates.

Summary Counts by Year

Table 3. Summary of Typical and Atypical Antipsychotics and Stroke in the Sentinel Distributed Database between January 1, 2008 and December 31, 2010 by Year

Year	New Users	Eligible Members[1]	New Episodes	Days At Risk	Years at Risk	Adjusted Dispensings	Raw Dispensings	Days Supplied	Amount Supplied	New Episodes with an Event	Eligible Member-Days[1]	Eligible Member Years[1]
Ischemic Stroke												
Typical Antipsychotics												
2008	7,318	191,531	7,318	435,402	1,192.1	7,746	7,746	230,664	365,169	5	29,714,745	81,354.5
2009	11,669	215,929	11,669	697,925	1,910.8	12,283	12,284	370,533	575,547	12	56,115,817	153,636.7
2010	5,733	181,814	5,733	333,266	912.4	5,934	5,934	178,814	275,104	2	52,320,846	143,246.7
Atypical Antipsychotics												
2008	5,342	191,531	5,342	314,868	862.1	5,484	5,484	167,421	284,231	5	29,714,745	81,354.5
2009	9,122	217,542	9,122	545,085	1,492.4	9,386	9,387	291,619	478,554	5	56,437,421	154,517.2
2010	5,006	185,584	5,006	289,686	793.1	5,107	5,108	157,749	256,723	0	53,224,717	145,721.3
Intracranial Hemorrhage												
Typical Antipsychotics												
2008	7,071	191,249	7,071	421,342	1,153.6	7,488	7,488	223,218	353,963	0	28,990,970	79,373.0
2009	11,302	215,865	11,302	676,659	1,852.6	11,897	11,898	359,173	556,422	1	54,757,842	149,918.8
2010	5,631	182,242	5,631	327,096	895.5	5,830	5,830	175,515	270,670	2	51,562,327	141,170.0
Atypical Antipsychotics												
2008	5,162	191,249	5,162	303,902	832.0	5,302	5,302	161,529	274,546	0	28,990,970	79,373.0
2009	8,845	217,430	8,845	529,185	1,448.8	9,099	9,100	283,298	464,256	0	55,052,960	150,726.8
2010	4,912	185,873	4,912	284,359	778.5	5,011	5,012	154,969	253,223	1	52,409,331	143,488.9

[1]Eligible Members, Member-Days, and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period

Summary Counts by Sex

Table 4. Summary of Typical and Atypical Antipsychotics and Stroke in the Sentinel Distributed Database between January 1, 2008 and December 31, 2010 by Sex

Sex	New Users	Eligible Members[1]	New Episodes	Days At Risk	Years at Risk	Adjusted Dispensings	Raw Dispensings	Days Supplied	Amount Supplied	New Episodes with an Event	Eligible Member-Days[1]	Eligible Member Years[1]
Ischemic Stroke												
Typical Antipsychotics												
Female	13,177	140,584	13,177	780,156	2,136.0	13,798	13,798	413,993	646,209	13	70,699,963	193,565.9
Male	11,543	134,878	11,543	686,437	1,879.4	12,165	12,166	366,018	569,611	6	67,451,445	184,672.0
Other	0	0	0	0	0.0	0	0	0	0	0	0	0.0
Atypical Antipsychotics												
Female	10,398	140,584	10,398	614,964	1,683.7	10,658	10,659	330,189	540,240	3	71,337,275	195,310.8
Male	9,072	134,878	9,072	534,675	1,463.9	9,319	9,320	286,600	479,268	7	68,039,608	186,282.3
Other	0	0	0	0	0.0	0	0	0	0	0	0	0.0
Intracranial Hemorrhage												
Typical Antipsychotics												
Female	12,780	140,512	12,780	757,302	2,073.4	13,381	13,381	401,711	626,103	2	69,220,817	189,516.3
Male	11,224	134,810	11,224	667,795	1,828.3	11,834	11,835	356,195	554,951	1	66,090,322	180,945.4
Other	0	0	0	0	0.0	0	0	0	0	0	0	0.0
Atypical Antipsychotics												
Female	10,106	140,512	10,106	597,851	1,636.8	10,356	10,357	321,108	525,719	0	69,815,671	191,144.9
Male	8,813	134,810	8,813	519,595	1,422.6	9,056	9,057	278,688	466,305	1	66,637,590	182,443.8
Other	0	0	0	0	0.0	0	0	0	0	0	0	0.0

[1]Eligible Members, Member-Days, and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period

Summary Counts by Age Group

Sentinel

Table 5. Summary of Typical and Atypical Antipsychotics and Stroke in the Sentinel Distributed Database between January 1, 2008 and December 31, 2010 by Age Group												
Age Group	New Users	Eligible Members[1]	New Episodes	Days At Risk	Years at Risk	Adjusted Dispensings	Raw Dispensings	Days Supplied	Amount Supplied	New Episodes with an Event	Eligible Member-Days[1]	Eligible Member Years[1]
Ischemic Stroke												
Typical Antipsychotics												
18-39	4,186	35,895	4,186	248,735	681.0	4,424	4,424	132,553	208,283	3	19,059,333	52,181.6
40-54	9,585	93,218	9,585	571,154	1,563.7	10,099	10,100	304,448	468,993	8	48,842,100	133,722.4
55-65	10,949	163,112	10,949	646,704	1,770.6	11,440	11,440	343,010	538,544	8	70,249,975	192,333.9
Atypical Antipsychotics												
18-39	3,141	35,895	3,141	183,465	502.3	3,214	3,215	97,693	161,229	4	19,294,889	52,826.5
40-54	7,384	93,324	7,384	434,722	1,190.2	7,615	7,615	233,557	378,916	3	49,376,179	135,184.6
55-65	8,945	163,308	8,945	531,452	1,455.0	9,148	9,149	285,539	479,363	3	70,705,815	193,582.0
Intracranial Hemorrhage												
Typical Antipsychotics												
18-39	4,075	35,884	4,075	242,248	663.2	4,305	4,305	129,060	203,352	1	18,686,759	51,161.6
40-54	9,314	93,198	9,314	555,627	1,521.2	9,817	9,818	296,104	454,983	2	47,836,512	130,969.2
55-65	10,615	163,017	10,615	627,222	1,717.2	11,093	11,093	332,742	522,720	0	68,787,868	188,330.9
Atypical Antipsychotics												
18-39	3,061	35,884	3,061	178,854	489.7	3,133	3,134	95,266	156,518	0	18,902,512	51,752.3
40-54	7,165	93,304	7,165	421,781	1,154.8	7,387	7,387	226,578	368,904	0	48,342,059	132,353.3
55-65	8,693	163,212	8,693	516,811	1,415.0	8,892	8,893	277,952	466,603	1	69,208,690	189,483.1

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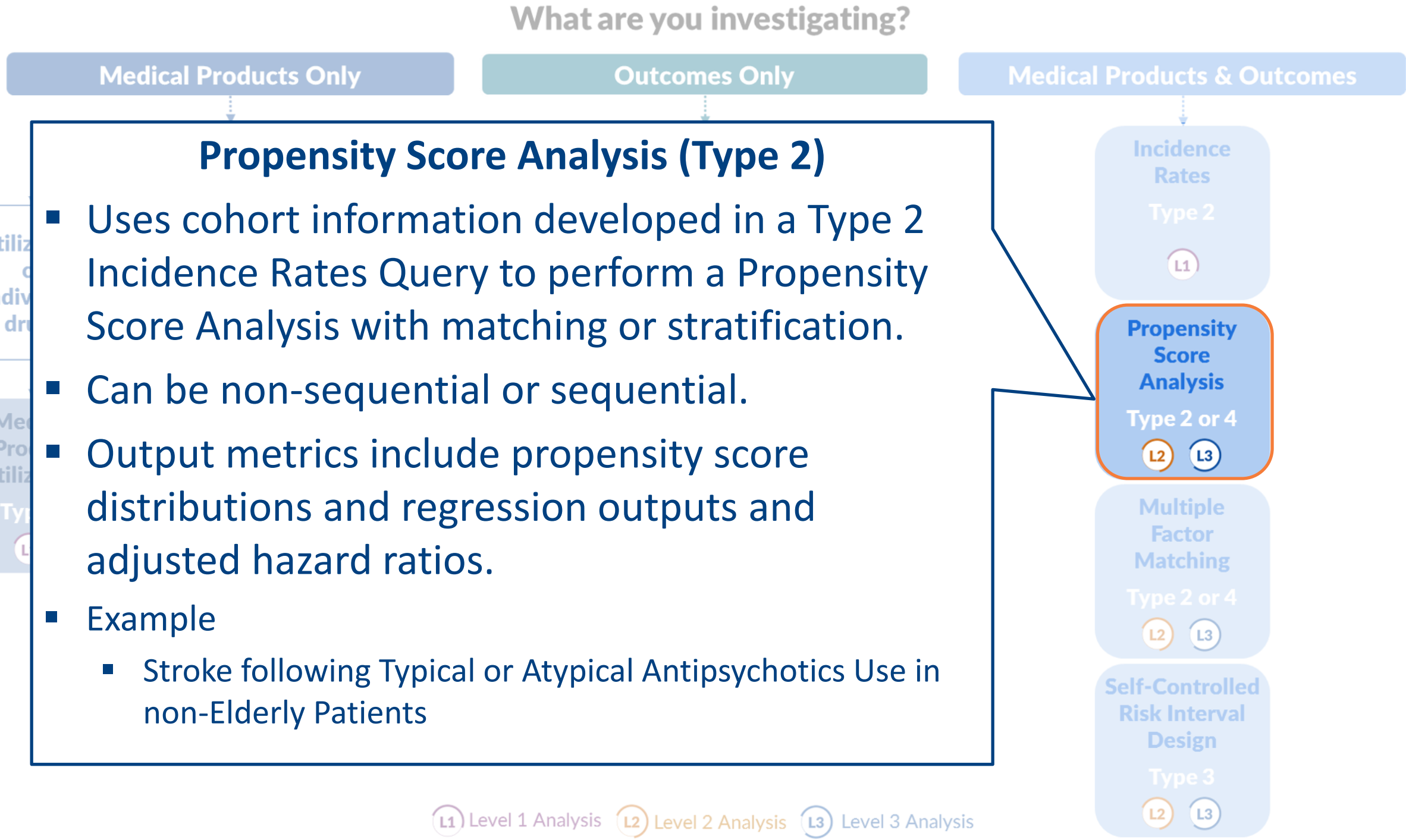
Propensity Score Analysis


What are you investigating?
Medical Products Only
Outcomes Only
Medical Products & Outcomes
Propensity Score Analysis (Type 2)
Uses cohort information developed in a Type 2 Incidence Rates Query to perform a Propensity Score Analysis with matching or stratification.
Can be non-sequential or sequential.
Output metrics include propensity score distributions and regression outputs and adjusted hazard ratios.
Example
Stroke following Typical or Atypical Antipsychotics Use in non-Elderly Patients
Incidence Rates
Type 2
L1
Propensity Score Analysis
Type 2 or 4
L2
L3
Multiple Factor Matching
Type 2 or 4
L2
L3
Self-Controlled Risk Interval Design
Type 3
L2
L3
L1 Level 1 Analysis
L2 Level 2 Analysis
L3 Level 3 Analysis

Propensity Score Match Design Diagram

Propensity Score
- 1:1 Matching
- Caliper: 0.05
- Age, Sex
- Recorded History Parameters

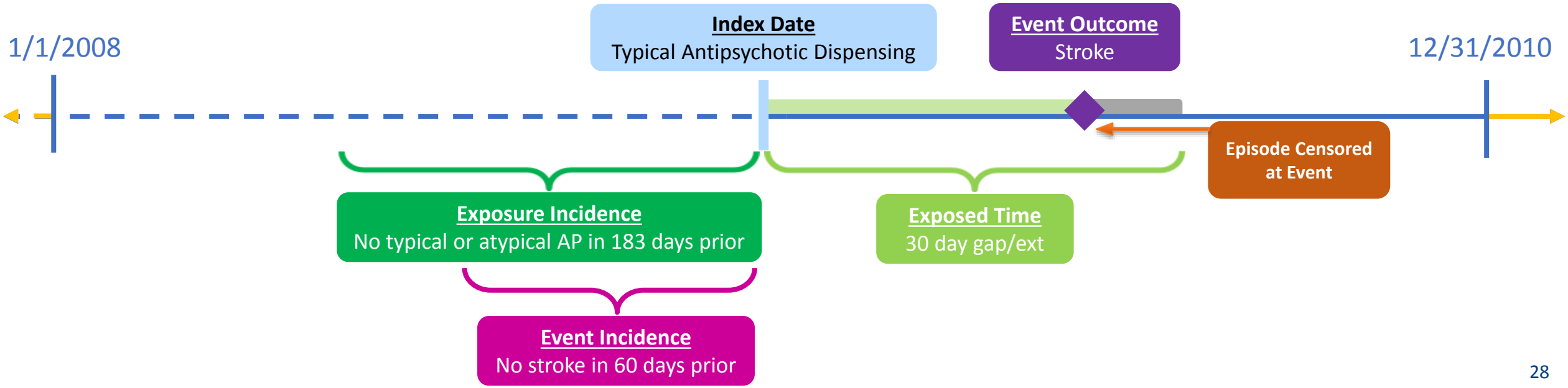
Covariate Evaluation Window
183 days to 1 day prior to index

Exclusion
Dementia 183 days to 0 day prior to index

Enrollment
183-day Enrollment
45 Day Enrollment Gap
Medical and Drug Coverage

Cohort Definition
First valid exposure episode; no cohort re-entry

Cohort Characteristics
- Include adults ages 18-65 at index
- Do not restrict sex or race
- No chart availability restrictions



Propensity Score Analysis

- By assigning an exposure of interest and comparator, the type 2 output can be leveraged in an inferential analysis to:
  - Assign members a **propensity score, based on user-defined criteria**
  - Calculate adjusted risk estimates using **matching or stratification**

- For each comparison, **Cox proportional hazards regression models** is used to estimate hazard ratios and corresponding 95% confidence intervals

- There is an option for risk-set level return, and patient-level return

Baseline Characteristics

Table 1a. Cohort of New Initiators of Typical Antipsychotics and Atypical Antipsychotics, Ischemic Stroke (Unmatched, Aggregated), Ratio: 1:1, Caliper:0.05

	Medical Product				Covariate Balance	
Characteristic	Typical Antipsychotics		Atypical Antipsychotics			
	N/Mean	%/Std Dev[1]	N/Mean	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients (N)	23,186	100.0%	17,797	100.0%	-	-
Demographics						
Mean age	51.6	10.6	52.0	10.5	-0.376	-0.036
Age: 18-39	3,899	16.8%	2,845	16.0%	0.830	0.022
Age: 40-54	8,954	38.6%	6,698	37.6%	0.983	0.020
Age: 55-65	10,333	44.6%	8,254	46.4%	-1.813	-0.036
Gender (Female)	12,358	53.3%	9,508	53.4%	-0.125	-0.003
Gender (Male)	10,828	46.7%	8,289	46.6%	0.125	0.003
Year (2008)	7,318	31.6%	5,342	30.0%	1.546	0.033
Year (2009)	11,034	47.6%	8,448	47.5%	0.120	0.002
Year (2010)	4,834	20.8%	4,007	22.5%	-1.666	-0.040
Recorded history of:						
Prior combined comorbidity raw score	0.0	0.0	0.0	0.0	0.000	-
AMI	3,138	13.5%	2,354	13.2%	0.307	0.009
Anxiety	3,745	16.2%	2,593	14.6%	1.582	0.044
Bipolar	6,233	26.9%	4,079	22.9%	3.963	0.092
Depression	7,030	30.3%	4,637	26.1%	4.265	0.095
Diabetes	13,582	58.6%	10,215	57.4%	1.181	0.024
Heart failure	6,795	29.3%	5,061	28.4%	0.869	0.019
Hypercholesterolemia	12,805	55.2%	9,621	54.1%	1.168	0.023
Hypertension	15,961	68.8%	11,907	66.9%	1.934	0.041
Kidney failure	7,009	30.2%	5,116	28.7%	1.483	0.033
Schizophrenia/psychotic	5,372	23.2%	3,416	19.2%	3.975	0.097
Substance abuse	2,178	9.4%	1,449	8.1%	1.252	0.044
Transient ischemic attack	941	4.1%	684	3.8%	0.215	0.011

Baseline Characteristics

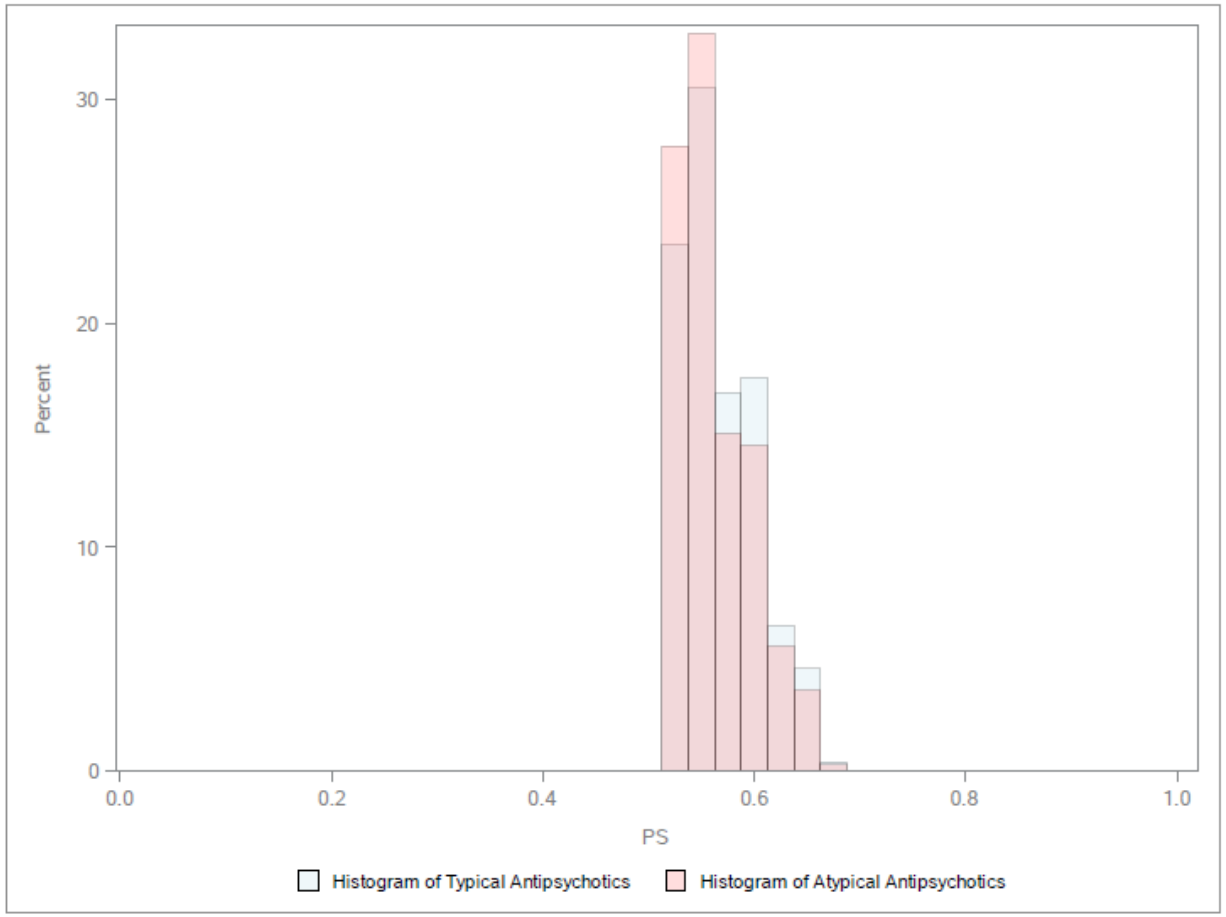
Sentinel

Table 1b. Cohort of New Initiators of Typical Antipsychotics and Atypical Antipsychotics, Ischemic Stroke (Matched, Aggregated), Ratio: 1:1, Caliper:0.05

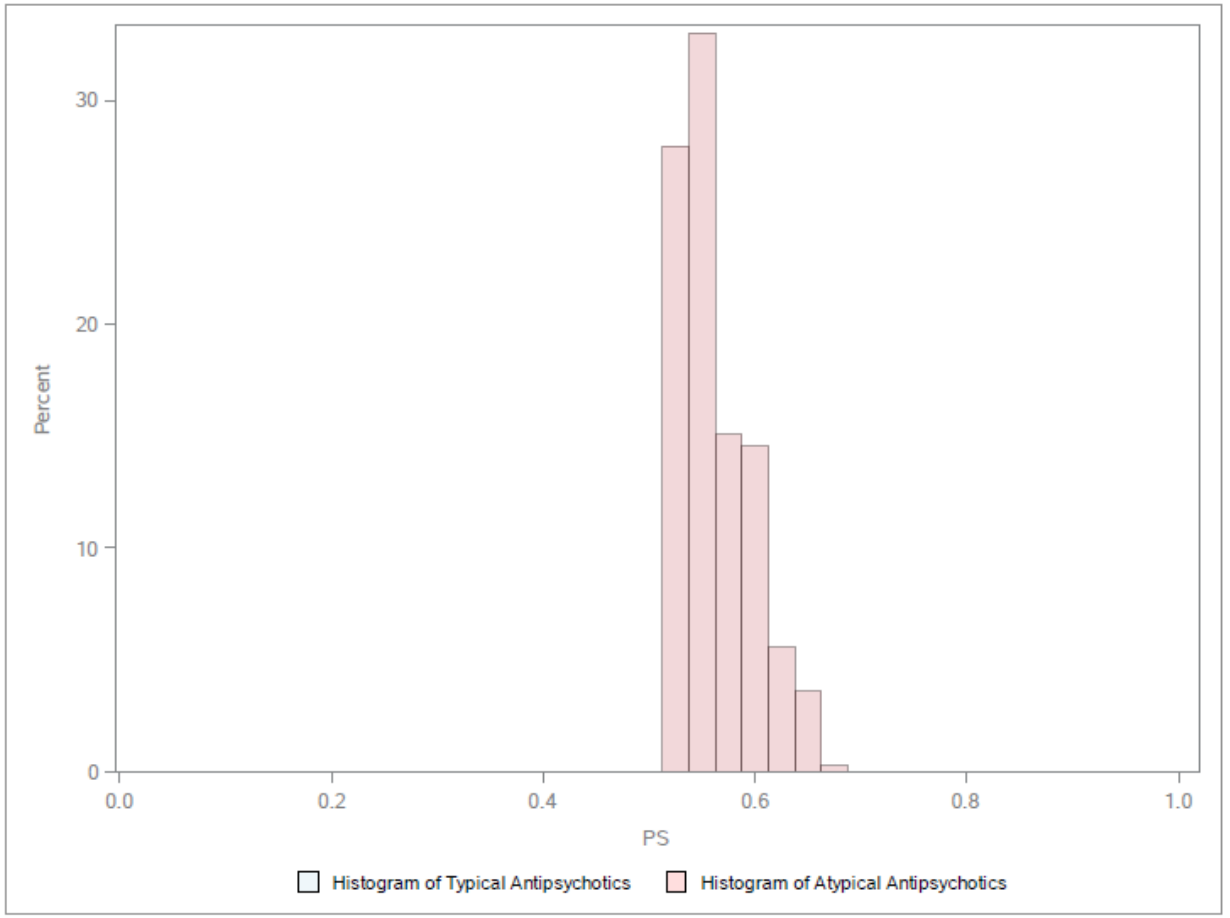
	Medical Product				Covariate Balance	
Characteristic	**Typical Antipsychotics**		**Atypical Antipsychotics**			
	N/Mean	**%/Std Dev[1]**	**N/Mean**	**%/Std Dev[1]**	**Absolute Difference**	**Standardized Difference**
Patients (N)	17,797	76.8%	17,797	100.0%	-	-
Demographics						
Mean age	52.0	10.5	52.0	10.5	0.033	0.003
Age: 18-39	2,820	15.8%	2,845	16.0%	-0.140	-0.004
Age: 40-54	6,733	37.8%	6,698	37.6%	0.197	0.004
Age: 55-65	8,244	46.3%	8,254	46.4%	-0.056	-0.001
Gender (Female)	9,548	53.6%	9,508	53.4%	0.225	0.005
Gender (Male)	8,249	46.4%	8,289	46.6%	-0.225	-0.005
Year (2008)	5,572	31.3%	5,342	30.0%	1.292	0.028
Year (2009)	8,421	47.3%	8,448	47.5%	-0.152	-0.003
Year (2010)	3,804	21.4%	4,007	22.5%	-1.141	-0.028
Recorded history of:						
Prior combined comorbidity raw score	0.0	0.0	0.0	0.0	0.000	-
AMI	2,359	13.3%	2,354	13.2%	0.028	0.001
Anxiety	2,624	14.7%	2,593	14.6%	0.174	0.005
Bipolar	4,040	22.7%	4,079	22.9%	-0.219	-0.005
Depression	4,624	26.0%	4,637	26.1%	-0.073	-0.002
Diabetes	10,206	57.3%	10,215	57.4%	-0.051	-0.001
Heart failure	5,063	28.4%	5,061	28.4%	0.011	0.000
Hypercholesterolemia	9,583	53.8%	9,621	54.1%	-0.214	-0.004
Hypertension	11,890	66.8%	11,907	66.9%	-0.096	-0.002
Kidney failure	5,086	28.6%	5,116	28.7%	-0.169	-0.004
Schizophrenia/psychotic	3,453	19.4%	3,416	19.2%	0.208	0.005
Substance abuse	1,434	8.1%	1,449	8.1%	-0.084	-0.003
Transient ischemic attack	708	4.0%	684	3.8%	0.135	0.007

Propensity Score Distribution

Histograms of Propensity Score Distribution Aggregated



Propensity score 1:1 Aggregated Matched Cohort, Matched Caliper = 0.05



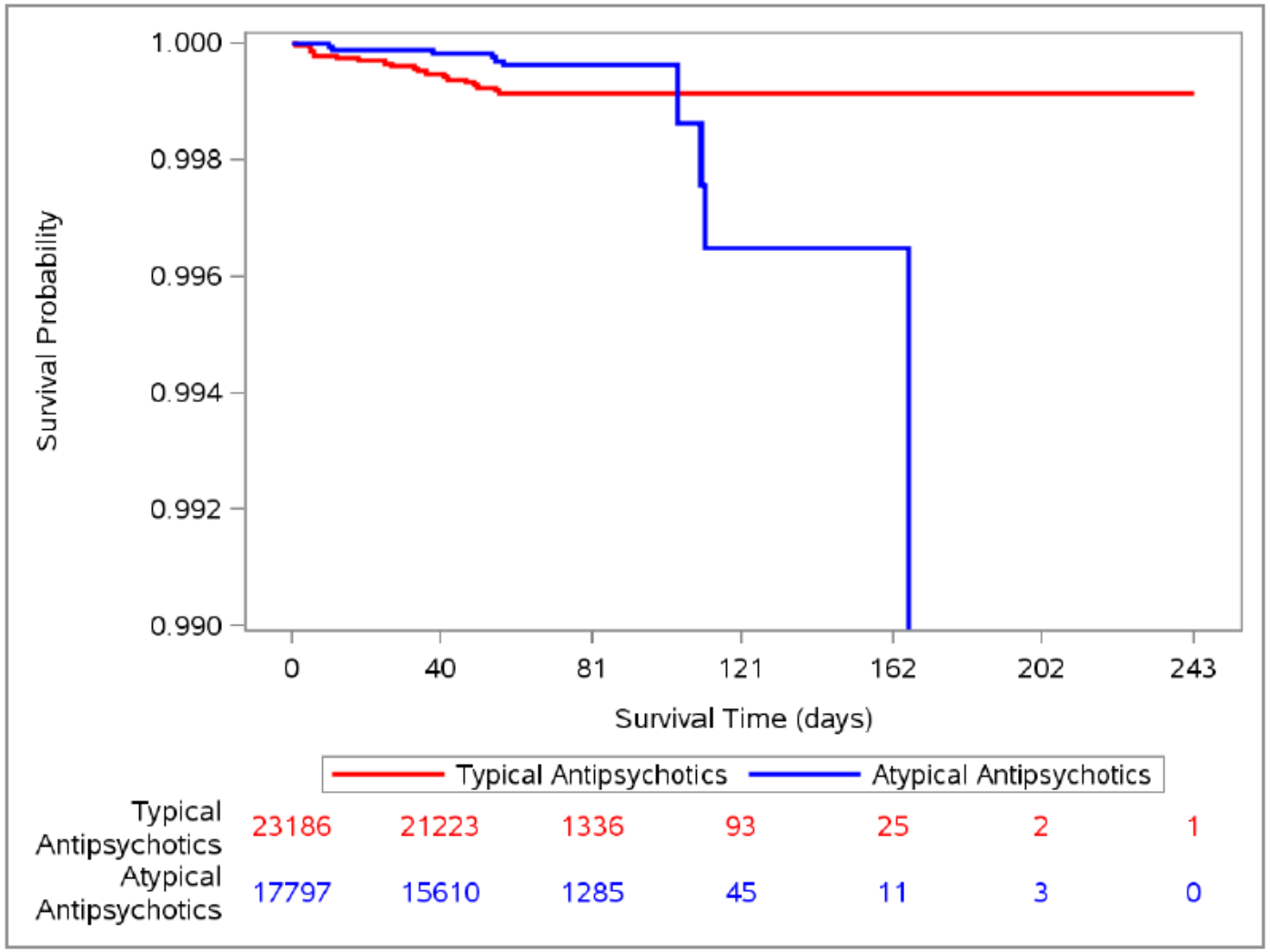
Risk Estimates

Table 2: Effect Estimates for Ischemic Stroke by Analysis Type

Medical Product	Number of New Users	Person Years at Risk	Average Person Days at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1000 Person Years	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person Years	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Typical Antipsychotics	23,186	3,768.57	59.37	0.16	19	5.04	0.82	1.58	0.26	1.48 (0.69, 3.20)	0.314
Atypical Antipsychotics	17,797	2,887.43	59.26	0.16	10	3.46	0.56				
1:1 Matched Conditional Predefined Analysis; Caliper= 0.05											
Typical Antipsychotics	17,797	2,579.38	52.94	0.14	14	5.43	0.79	3.10	0.45	2.33 (0.90, 6.07)	0.082
Atypical Antipsychotics	17,797	2,579.38	52.94	0.14	6	2.33	0.34				
1:1 Matched Unconditional Predefined Analysis; Caliper= 0.05											
Typical Antipsychotics	17,797	2,886.62	59.24	0.16	15	5.20	0.84	1.73	0.28	1.54 (0.69, 3.43)	0.293
Atypical Antipsychotics	17,797	2,887.43	59.26	0.16	10	3.46	0.56				

Kaplan Meyer Survival Curve

Kaplan Meier Survival Curves of Events and Followup Time for Ischemic Stroke, Full Cohort.



Attrition Table – Proposed revision

- Reports the initial member count in a population
- Reports the loss in eligible members due to required enrollment coverage, inclusion and exclusion criteria, incidence washout, etc.

	Remaining	*Excluded*
Members meeting enrollment and demographic requirements		
Enrolled at any point during the query period		
Had required coverage type(s)		
Enrolled during specified age range		
Had requestable medical charts		
Met demographic requirements		
Members with a valid index event		
Had any cohort-defining claim		
Claim recorded during specified age range		
Met all episode definitions		
Met episode incidence requirement		
Had single NDC on index date		
Members with required pre-index history		
Had sufficient pre-index continuous enrollment		
Met event incidence criteria		
Had no recorded history of exclusion condition(s)		
Had recorded history of inclusion condition(s)		

Questions?

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Case Study 1: Antipsychotics and Stroke

A Journey from Summary Table to Propensity Score Analysis

Ting-Ying Jane Huang, PhD

Sentinel Operations Center

4/4/2019

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DEPARTMENT OF POPULATION MEDICINE

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Sentinel

Many thanks are due to the Data Partners who provided the data used in these analyses

Outline

- Safety question
- Background rate: drug utilization
- Feasibility assessment: incidence rate in target population
- Comparative assessment: propensity score analysis
- Regulatory actions and publications

Safety Question

- In 2016, the FDA considered a proposed label change for warning/precaution regarding cerebrovascular events associated with antipsychotic use

Typical Antipsychotics
1. Prochlorperazine (Compazine)
2. Haloperidol (Haldol)
3. Loxapine (Loxitane)
4. Thioridazine (Mellaril)
5. Molindone (Moban)
6. Thiothixene (Navane)
7. Pimozide (Orap)
8. Fluphenazine (Prolixin)
9. Trifluoperazine (Stelazine)
10. Chlorpromazine (Thorazine)
11. Perphenazine (Trilafon)

Atypical Antipsychotics
1. Aripiprazole (Abilify)
2. Asenapine (Saphris)
3. Clozapine (Clozaril)
4. Iloperidone (Fanapt)
5. Lurasidone (Latuda)
6. Olanzapine (Zyprexa)
7. Olanzapine/fluoxetine (Symbyax)
8. Paliperidone (Invega)
9. Quetiapine (Seroquel)
10. Risperidone (Risperdal)
11. Ziprasidone (Geodon)

Existing language in safety label regarding cerebrovascular risk among elderly patients with dementia

Study	Population	Risk estimate (95% CI), stroke	Comparison
Cohort studies			
Barnett (2007)	Dementia	1.29 (0.48-3.47)	FGAs: unexposed
Gill (2005)	Dementia	1.01 (0.81-1.26)	Atypical:Typical
Hermann (2004)	65+ years old	1.1 (0.5-2.3)	Olanzapine: Typical
"	"	1.4(0.7-2.8)	Risperidone:Typical
Sacchetti (2008)	65+ years old	**2.34 (1.01-5.41)**	Phenothiazines:Atypical
Shin (2015a)	65+ years old	**3.47 (1.97-5.48)**	Chlorpromazine:Risperidone
Vasilyeva (2013)	65+ years old	1.14 (0.96-1.34)	SGA:FGA
Wang (2007)	Medicare	**1.09 (1.02-1.16)**	Typical:Atypical
Case-control			
Liperoti (2005)	Dementia	1.24 (0.95-1.63)	Conventional:unexposed
Hsieh (2013)	Schizophrenia	**2.75 (1.34-5.64)**	FGA:unexposed
Kleijer (2009)	50+ years old	**2.6 (1.3-5.0)**	Conventional:atypical
Laredo (2011)	Dementia	**1.46 (1.30-1.64)**	Typical: unexposed
Self-controlled			
Douglas (2008)	Stroke patients	**1.69 (1.55-1.84)**	Typical:unexposed
Pratt (2010)	65+ y.o. with stroke	**2.7 (1.8-4.0)**	Typical:unexposed
Wu (2013)	Stroke patients	**1.91 (1.67-2.18)**	SGA:FGA
"	"	**1.43 (1.34-1.51)**	FGA: unexposed
"	"	**2.3 (2.2-2.5)**	Prochlorperazine:unexposed

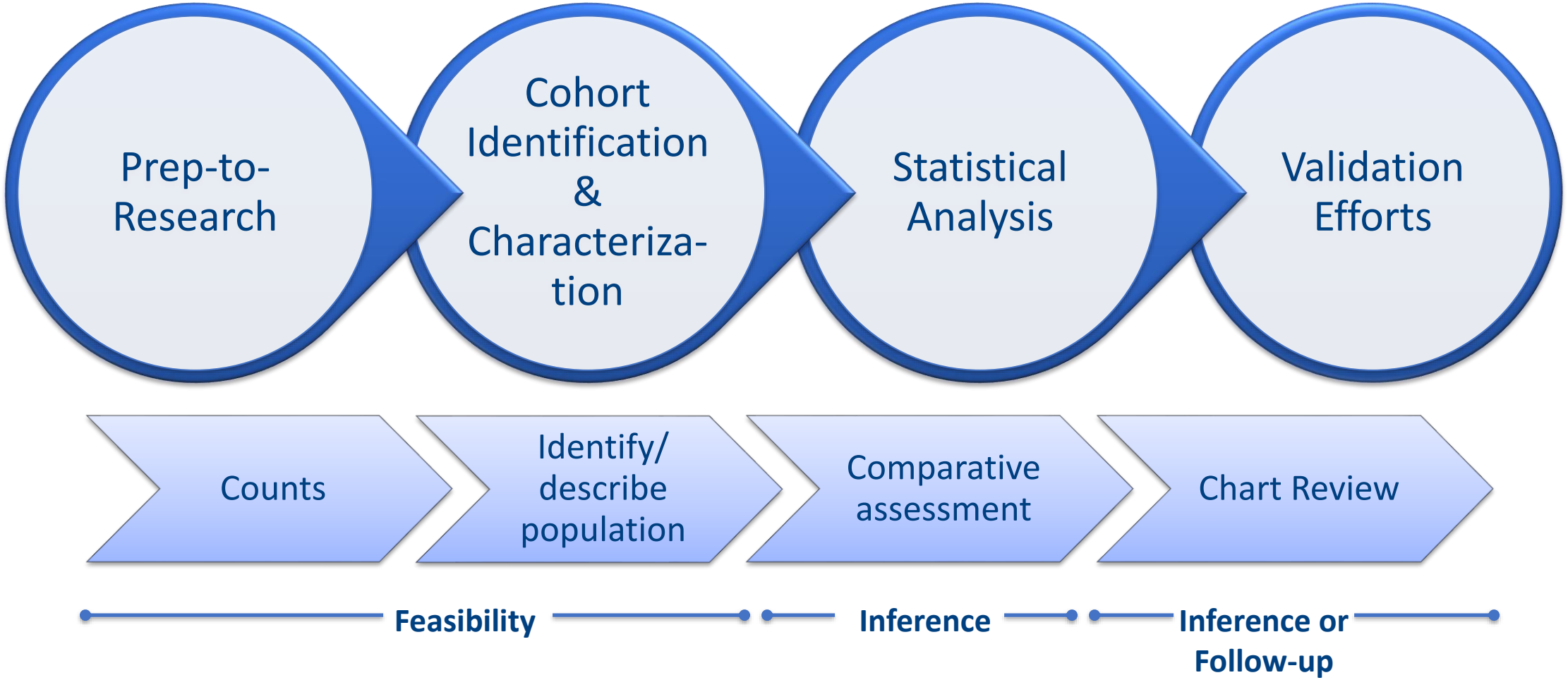
FGA first generation antipsychotics, SGA second generation antipsychotics

Study Questions

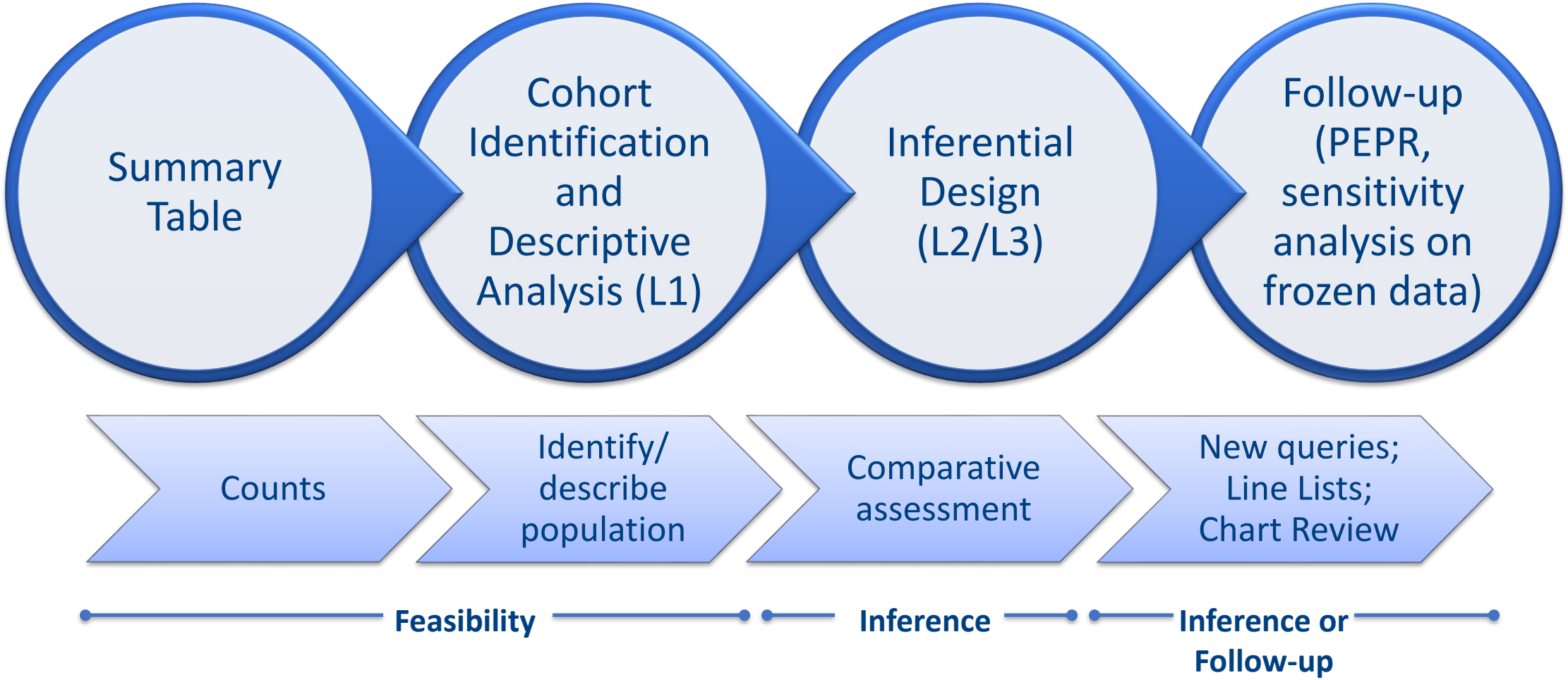
- Do younger (<65 years), non-demented users of typical antipsychotics (APs) have a higher risk of stroke, compared to users of atypical APs?
- Does AP dose modify this risk, haloperidol in particular?
- Is the risk highest in the first few days/weeks after initiating APs?

- Do concomitant users of atypical APs and antidepressants have a higher risk of stroke, compared to users of only antidepressants?

Typical Pharmacoepidemiologic Study

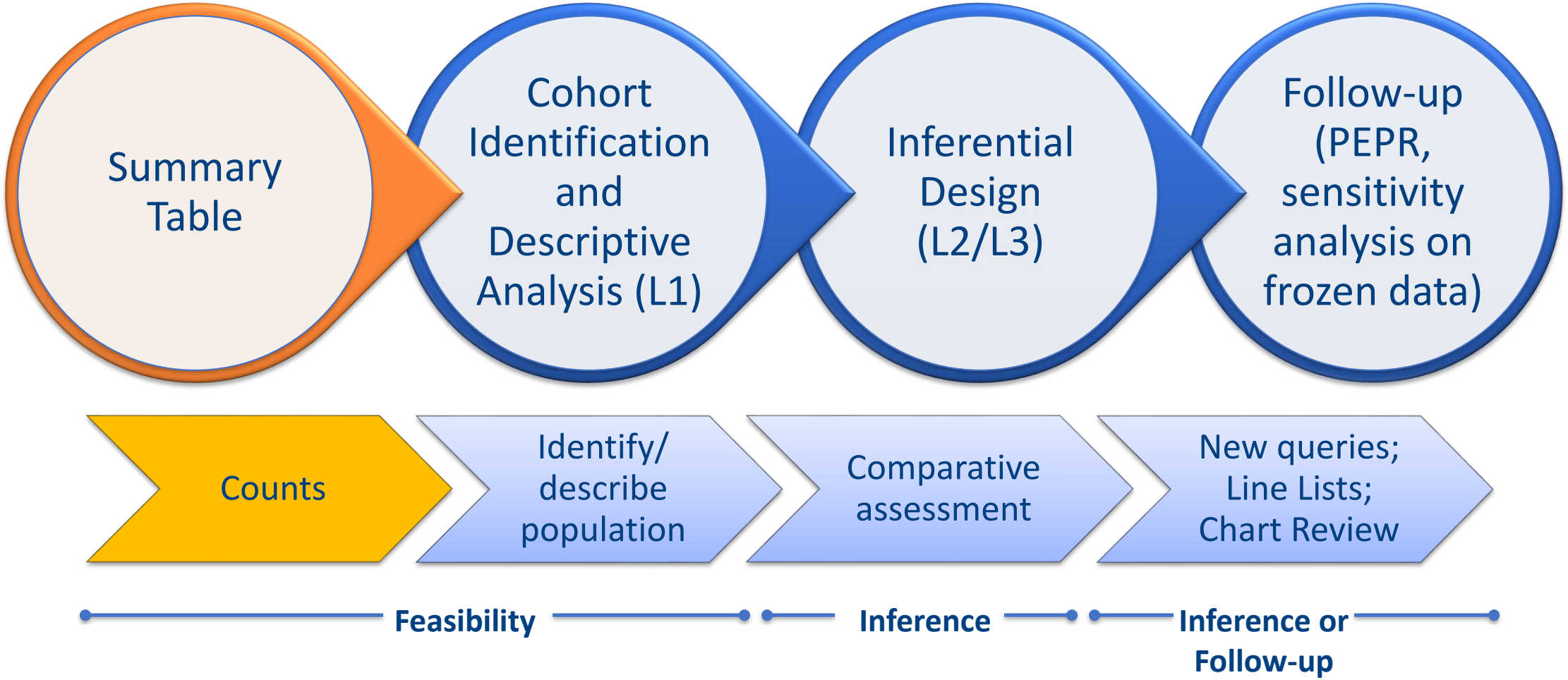


Safety Assessment in Sentinel



PEPR: Patient Episode Profile Retrieval

Safety Assessment in Sentinel



PEPR: Patient Episode Profile Retrieval

Summary Table

SURVEILLANCE TOOLS

- Active Risk Identification and Analysis (ARIA)
- Signal Identification in the Sentinel System
- Routine Querying Tools
  - Level 1 Modular Program Queries
  - Level 2 Modular Program Queries
  - Level 3 Modular Program Queries
  - Summary Table Queries
- Software Toolkits
- Health Outcome of Interest Validations and Literature Reviews

Summary Table Queries

Summary Table Queries are very simple queries on counts, prevalence, and incidence of drug products, diagnosis codes, and procedure codes stratified by year, sex, age group, and where appropriate, setting of care.

Documents	*Description*	*Links*
Sentinel Distributed Query Tool	Sentinel uses PopMedNet, an open-source software application, to enable the operation and governance of the secure Sentinel distributed data network. The PopMedNet software facilitates secure distribution and response of all Sentinel distributed queries, enables monitoring of query activity, and provides a single point of contact for Sentinel Data Partners for all Sentinel querying activity. The Sentinel Distributed Query Tool implementation is compliant with Federal Information Security Management Act (FISMA) Moderate level as defined by NIST SP 800-53 Revision 4, Recommended Security Controls for Federal Information Systems.	Sentinel Distributed Query Tool / PopMedNet Documentation
Distributed Query Tool Summary Table Descriptions (v2.0)	The Sentinel Query Tool Summary Table Description delineates the structure of the summary tables that are currently supported by the query tool.	Distributed Query Tool Summary Table Descriptions v2.0

Summary Table

Sentinel Distributed Query Tool Summary Table Descriptions

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Summary Table

Sentinel Distributed Query Tool Summary Table Descriptions

Table of Contents

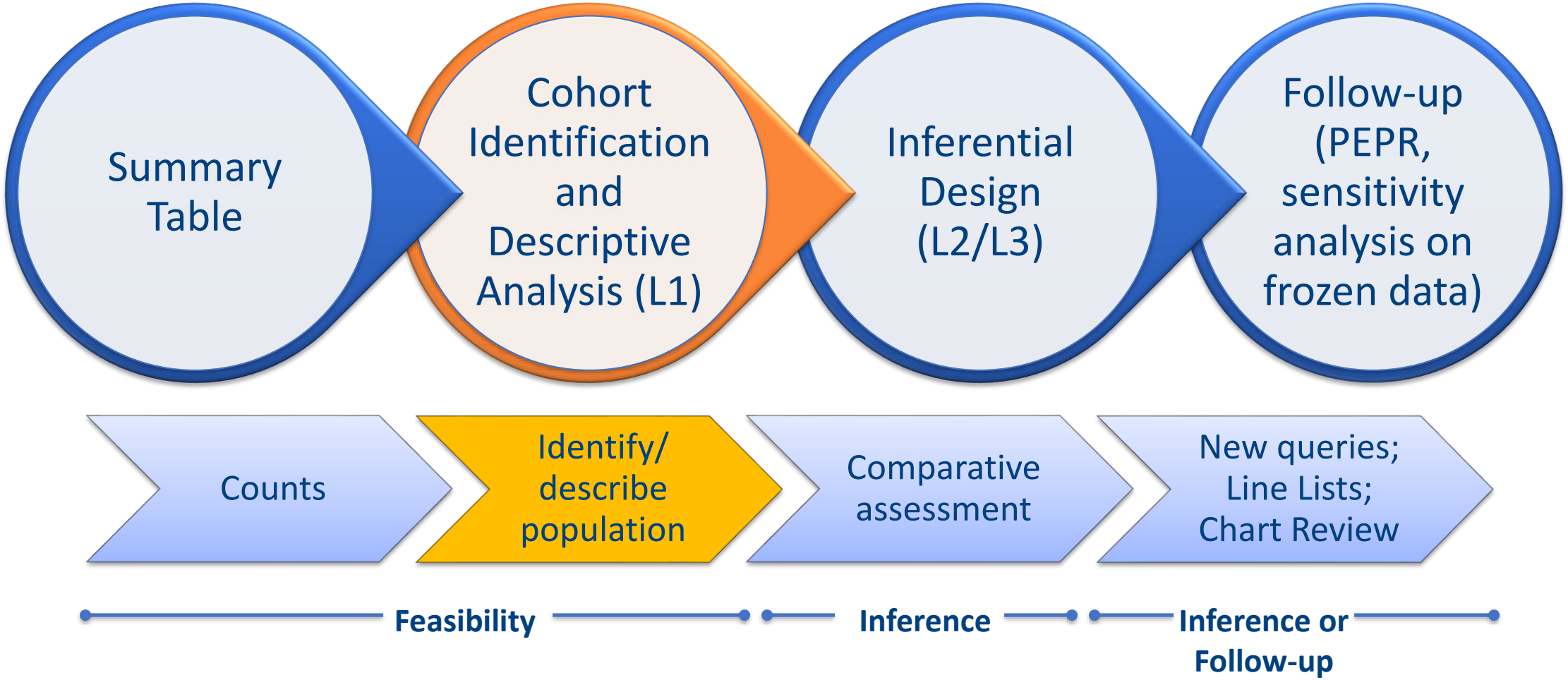
Summary Table Results

Table 1. Number of Prevalent OLANZAPINE Users, Number of Dispensings, and Total Days Supplied by Year, Sex, and Age Group

Generic Name	OLANZAPINE	Selecting generic name here will update table below. Select only one generic name.

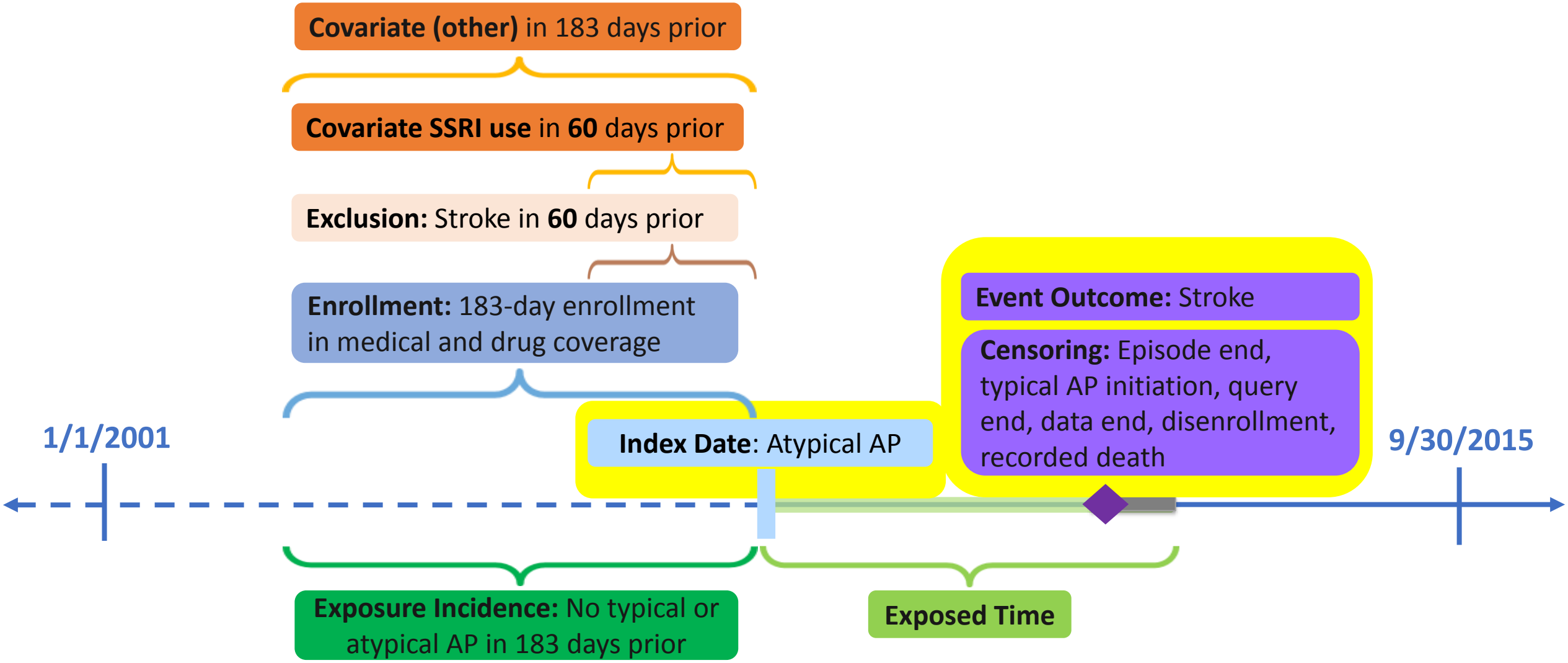
			Data		
Year	Sex	Age Group	Number of Users	Number of Dispensings	Days Supplied
2010	M	19-21	1,286	5,289	169,115
		22-44	7,150	34,822	1,170,166
		45-64	7,400	39,889	1,406,770
		65-74	1,528	7,747	287,870
		75+	1,900	8,751	300,611
	F	19-21	624	2,040	63,607
		22-44	6,970	27,797	918,213
		45-64	9,477	47,545	1,710,644
		65-74	2,548	13,923	506,209
		75+	4,449	24,823	853,600
2011	M	19-21	1,436	5,830	183,938
		22-44	7,146	35,540	1,196,473

Safety Assessment in Sentinel



PEPR: Patient Episode Profile Retrieval

L1: Feasibility Assessment (CIDA Type 2)



L1 Results

Table 1: Baseline Characteristics of Patients Exposed to Atypical or Typical Antipsychotics, Scenarios with Outcome = Ischemic Stroke

	Atypical		Typical		Haloperidol	
	N|Mean	%|Std	N|Mean	%|Std	N|Mean	%|Std
Number of patients	1,241,864		148,229		81,883	
Age	48.6	19	62.4	18.3	70	17.9
Age: 18-39	474,808	38.2%	24,654	16.6%	8,590	10.5%
Age: 40-54	348,067	28.0%	29,237	19.7%	9,914	12.1%
Age: 55+	418,989	33.7%	94,338	63.6%	63,379	77.4%
Female	756,054	60.9%	71,550	48.3%	45,671	55.8%
Haloperidol Low (0.5-2 mg)					55,087	67.3%
Haloperidol Medium (5-10 mg)					11,749	14.3%
Haloperidol High (20 mg)					104	0.1%
Haloperidol Liquid					15,314	18.7%
Stroke in prior 3-6 months	16,549	1.3%	3,218	2.2%	2,404	2.9%
SSRI in prior 3-6 months	412,230	33.2%	29,677	20.0%	17,784	21.7%
Acute Myocardial Infarction	36,416	2.9%	11,227	7.6%	8,447	10.3%
Diabetes	154,252	12.4%	31,619	21.3%	19,554	23.9%
Heart Failure	63,400	5.1%	18,954	12.8%	15,586	19.0%
Hypercholesterolemia	283,670	22.8%	47,336	31.9%	27,506	33.6%
Hypertension	383,517	30.9%	70,546	47.6%	44,579	54.4%
Kidney Failure	71,968	5.8%	23,285	15.7%	18,059	22.1%
Transient Iischemic Attack	14,457	1.2%	2,864	1.9%	2,135	2.6%

L1 Results

Table 1: Baseline Characteristics of Patients Exposed to Atypical or Typical Antipsychotics, Scenarios with Outcome = Ischemic Stroke

	Atypical		Typical		Haloperidol	
	N|Mean	%|Std	N|Mean	%|Std	N|Mean	%|Std
Number of patients	1,241,864		148,229		81,883	
Age	48.6	19	62.4	18.3	70	17.9
Age: 18-39	474,808	38.2%	24,654	16.6%	8,590	10.5%
Age: 40-54	348,067	28.0%	29,237	19.7%	9,914	12.1%
Age: 55+	418,989	33.7%	94,338	63.6%	63,379	77.4%
Female	756,054	60.9%	71,550	48.3%	45,671	55.8%
Haloperidol Low (0.5-2 mg)					55,087	67.3%
Haloperidol Medium (5-10 mg)					11,749	14.3%
Haloperidol High (20 mg)					104	0.1%
Haloperidol Liquid					15,314	18.7%
Stroke in prior 3-6 months	16,549	1.3%	3,218	2.2%		
SSRI in prior 3-6 months	412,230	33.2%	29,677	20.0%		
					15,586	19.0%
Hypercholesterolemia	283,070	22.8%	47,336	31.9%	27,506	33.6%
Hypertension	383,517	30.9%	70,546	47.6%	44,579	54.4%
Kidney Failure	71,968	5.8%	23,285	15.7%	18,059	22.1%
Transient Iischemic Attack	14,457	1.2%	2,864	1.9%	2,135	2.6%

1. Product strength, but not daily dose, of index exposure is readily available in SCDM
2. Comparative analyses stratified by index exposure product strength may experience sample size issue

How many AP users with stroke history do we lose if we extend stroke exclusion from 2 to 6 months prior to index date?

How many concomitant SSRI users do we gain if we extend the concomitancy definition from 2 to 6 months prior to index date?

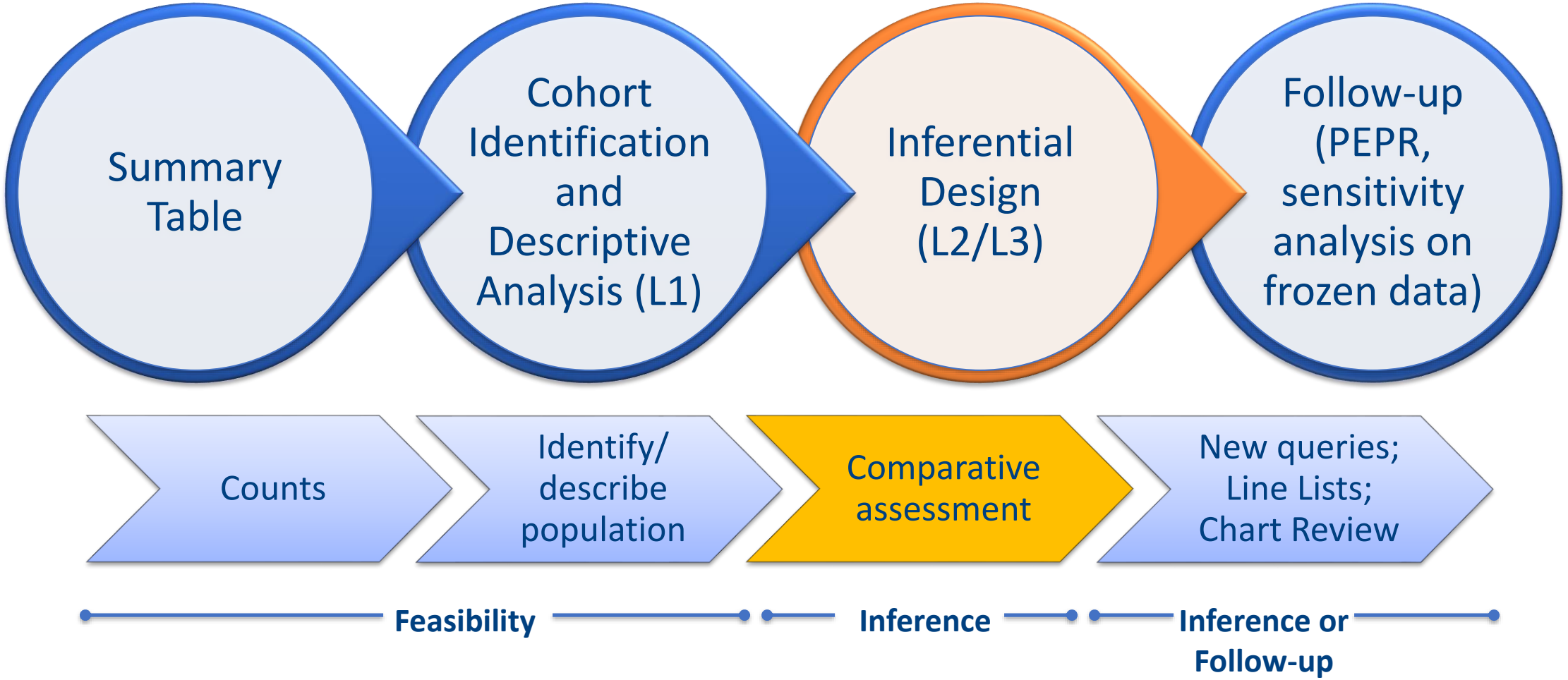
L1 Results

Table 4: Summary of Stroke following Treatment with Atypical or Typical Antipsychotics, with or without Selective Serotonin Reuptake Inhibitors (SSRIs) in the Sentinel Distributed Database between January 1, 2001 and September 30,

Scenarios with Outcome = Ischemic Stroke

	New Users	Years at Risk	New Users w/ Outcome	New Users w/ Outcome / 10K Years at Risk
Atypical Antipsychotics and Ischemic Stroke				
	1,241,864	631,084.5	2,669	42.29
Typical Antipsychotics and Ischemic Stroke				
	148,229	35,356.6	339	95.88
Haloperidol and Ischemic Stroke				
	81,883	17,602.5	247	140.32

Safety Assessment in Sentinel



PEPR: Patient Episode Profile Retrieval

Study Questions

- Do younger (<65 years), non-demented users of typical antipsychotics (APs) have a higher risk of stroke, compared to users of atypical APs?
- Does AP dose modify this risk, haloperidol in particular?
- Is the risk highest in the first few days/weeks after initiating APs?

- Do concomitant users of atypical APs and antidepressants have a higher risk of stroke, compared to users of only antidepressants?

Study Questions

- Do younger (<65 years), non-demented users of typical antipsychotics (APs) have a higher risk of stroke, compared to users of atypical APs?
- Does AP dose modify this risk, haloperidol in particular?
- Is the risk highest in the first few days/weeks after initiating APs?

Study Questions

- Do younger (<65 years), non-demented users of typical antipsychotics (APs) have a higher risk of stroke, compared to users of atypical APs?

- Is the risk highest in the first few days/weeks after initiating APs?

Study Questions

Specifications for Request ID cder_mpl2p_wp004

The Center for Drug Evaluation and Research has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) tool with Propensity Score Matching (PSM) to investigate the risk of ischemic and hemorrhagic stroke among new users of typical antipsychotics compared to new users of atypical antipsychotics with varying risk windows.

Query Period: January 1, 2001 - September 30, 2015
Coverage Requirement: Medical and Drug Coverage
Enrollment Requirement: 183 days
Enrollment Gap: 45 Days
Age Group(s): 18-64 years

	Exposure/Comparator Pair 1		Exposure/Comparator Pair 2		Exposure/Comparator Pair 3		Exposure/Comparator Pair 4	
Drug/Exposure								
Incident Exposure/Comparator	All typical antipsychotics	All atypical antipsychotics	All typical antipsychotics (risk window = 1-15 days)	All atypical antipsychotics (risk window = 1-15 days)	All typical antipsychotics (risk window = 16-90 days)	All atypical antipsychotics (risk window = 16-90 days)	Haloperidol	All atypical antipsychotics
Incident w/ Respect to:	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics	All atypical and typical antipsychotics
Washout	183 days	183 days	183 days	183 days	183 days	183 days	183 days	183 days
Cohort Definition	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period	Cohort includes only the first valid incident treatment episode during the query period
Episode Gap	30 days	30 days	30 days	30 days	30 days	30 days	30 days	30 days
Episode Extension Period	None	None	None	None	None	None	None	None
Minimum Episode Duration	1 day	1 day	1 day	1 days	16 days	16 days	1 day	1 day
Maximum Episode Duration	None	None	15 days	15 days	90 days	90 days	None	None
Episode Truncation for Exposure	All atypical antipsychotics	All typical antipsychotics	All atypical antipsychotics	All typical antipsychotics	All atypical antipsychotics	All typical antipsychotics	All atypical and typical antipsychotics (except Haloperidol)	All typical antipsychotics
Inclusion/Exclusion								
Pre-Existing Condition	Dementia	Dementia	Dementia	Dementia	Dementia	Dementia	Dementia	Dementia
Include/Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude	Exclude
Care Settings/PDX	Any	Any	Any	Any	Any	Any	Any	Any

Study Questions

- Do younger (<65 years), non-demented users of typical antipsychotics (APs) have a higher risk of stroke, compared to users of atypical APs?
- Is the risk highest in first few days/weeks after initiating APs?
- Do concomitant users of atypical APs and antidepressants have a higher risk of stroke, compared to users of only antidepressants?

Study Questions

- Do concomitant users of atypical APs and antidepressants have a higher risk of stroke, compared to users of only antidepressants?

Comparative Assessment

- Do concomitant users of atypical APs and antidepressants have a higher risk of stroke, compared to users of only antidepressants?

Comparative Assessment

Compare AP users

to whom?

- Do concomitant users of atypical APs and antidepressants have a higher risk of stroke, compared to users of only antidepressants?

Comparative Assessment

Options for the comparator group

1. AP users themselves: self-controlled design
2. Non-users: exact match on age, sex, and/or calendar time
3. Antidepressant users: prevalent new user design
4. Negative controls: users of another drug class with similar indications but no known associated risk for stroke

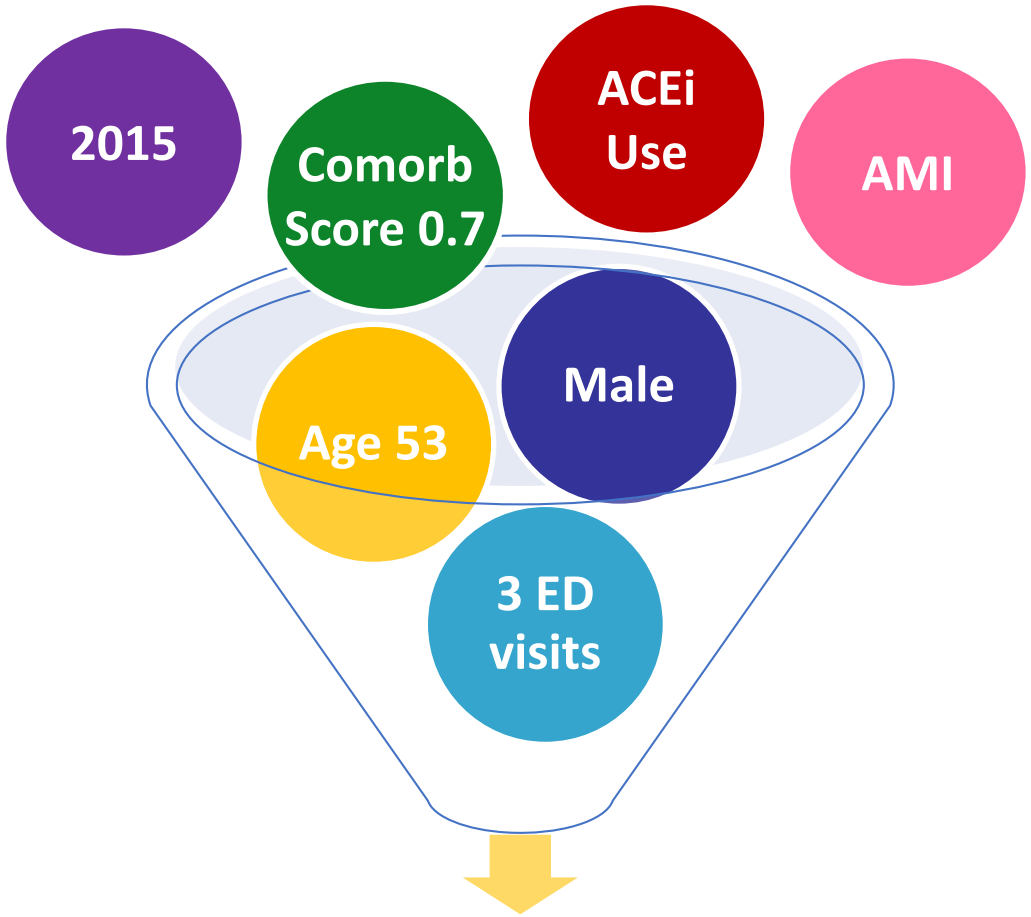
Comparative Assessment

Options for the comparator group

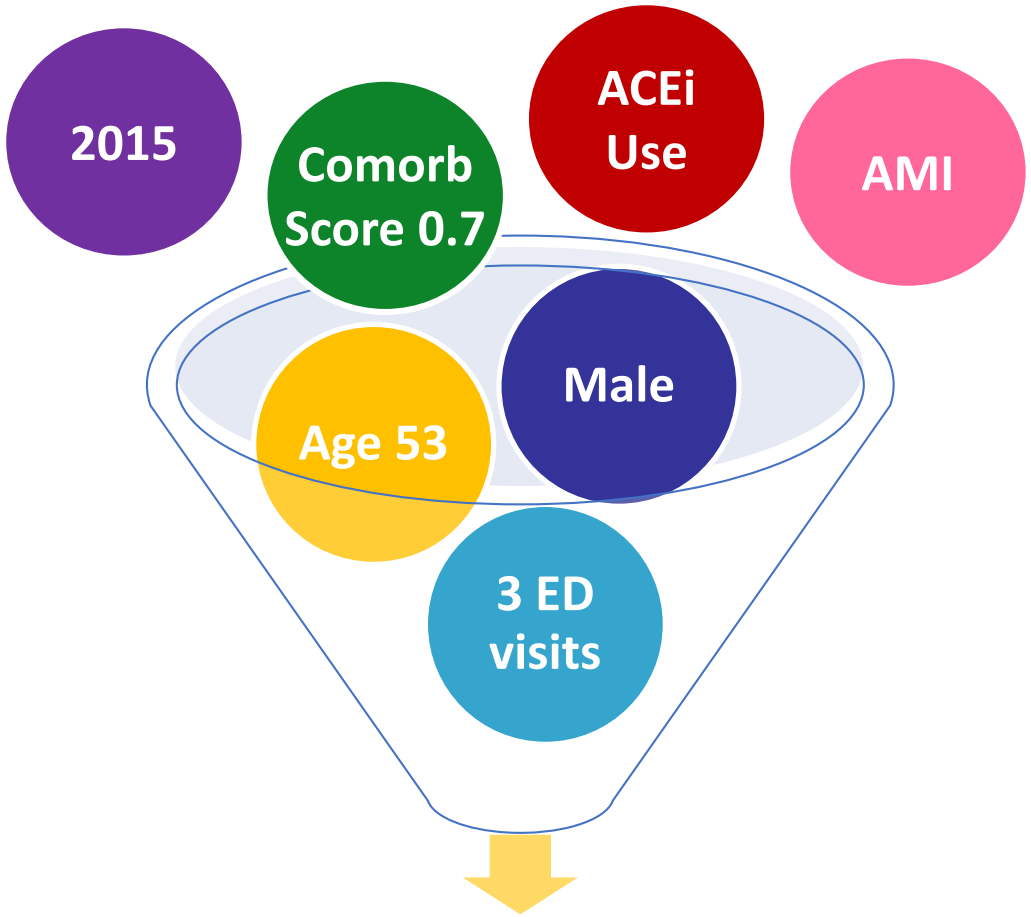
1. AP users themselves: self-controlled design
2. Non-users: exact match on age, sex, and/or calendar time
3. Antidepressant users: prevalent new user design
4. **Negative controls: users of another drug class with similar indications but no known associated risk for stroke**
   - Z-hypnotics: non-benzodiazepine hypnotics zolpidem, eszoplicone, zaleplon, used in treatment of insomnia

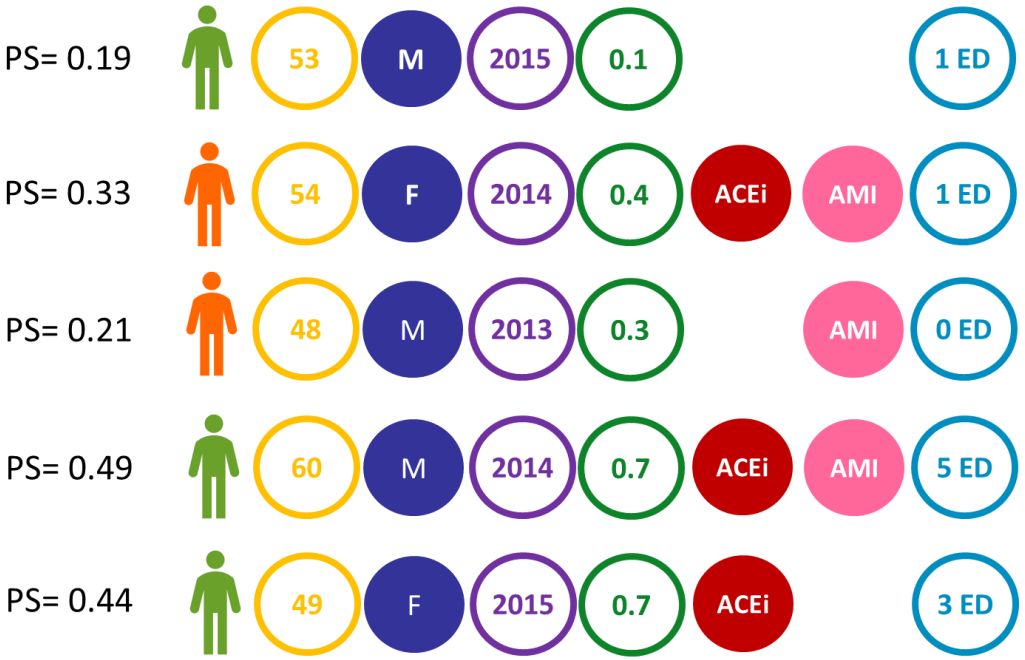
→ Final comparison: AP users vs z-hypnotic users, with existing SSRI use at baseline

1:1 Propensity Score Matching

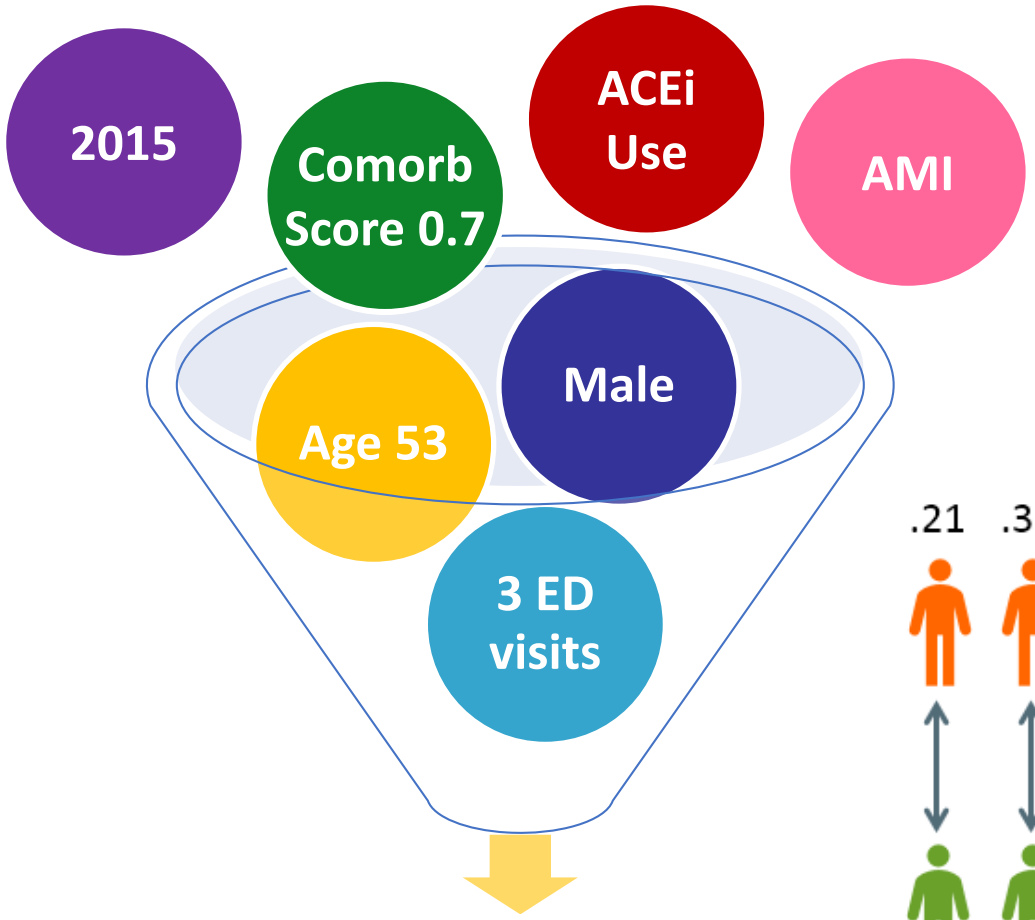


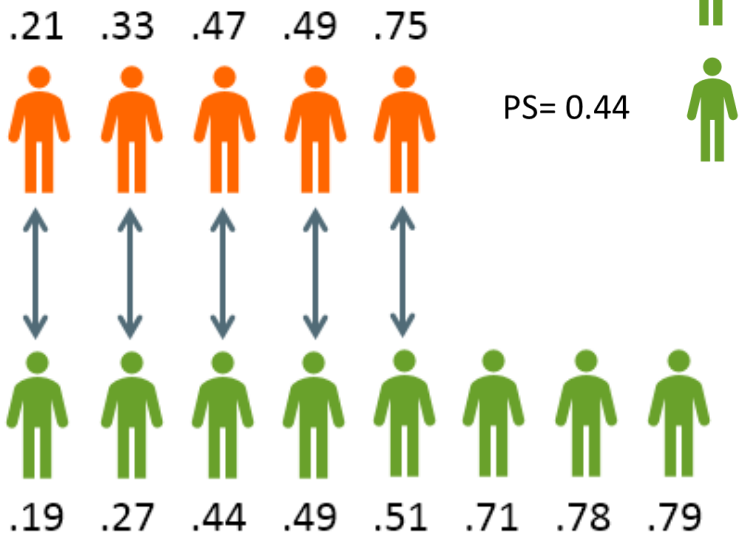
1:1 Propensity Score Matching

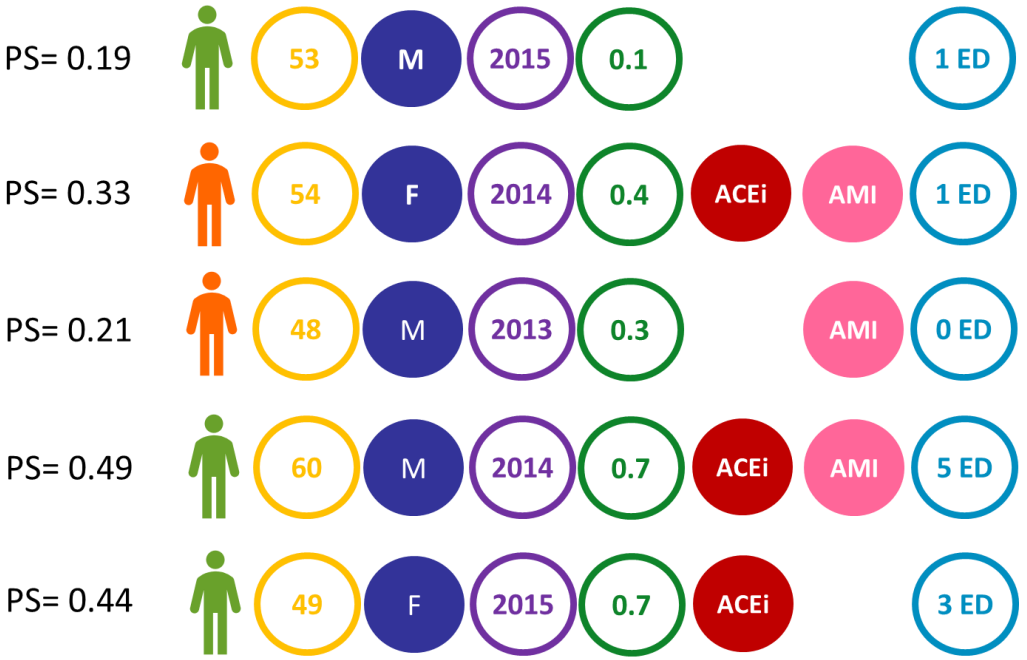




1:1 Propensity Score Matching







https://www.sentinelinitiative.org/communications/sentinel-initiative-events/sentinel-initiative-public-workshop-tenth-annual-day-2

L2 Results: Typical vs Atypical APs

Baseline Characteristics
Unmatched & Matched Cohorts

	Unmatched			Matched		
Selected characteristics	**Typical AP N (%/SD*)**	**Atypical AP N (%/ SD*)**	**Std Diff**	**Typical AP N (%/ SD*)**	**Atypical AP N (%/ SD*)**	**Std Diff**
Total	45,576	806,611		45,495	45,495	
Mean age	44.0 (12.6*)	39.9 (12.8*)	0.324	44.0 (12.6*)	44.2 (12.7*)	-0.020
Female	21,206 (46.5)	489,469 (60.7)	-0.287	21,194 (46.6)	20,987 (46.1)	0.009
Afib/flutter	648 (1.4)	4,745 (0.6)	0.084	620 (1.4)	660 (1.5)	-0.007
AMI	899 (2.0)	7,789 (1.0)	0.084	879 (1.9)	928 (2.0)	-0.008
Diabetes	5,226 (11.5)	52,950 (6.6%)	0.172	5,182 (11.4)	5,393 (11.9)	-0.014
HTN	9,800 (21.5)	120,258 (14.9)	0.171	9,754 (21.4)	9,886 (21.7)	-0.007
Renal failure	1,869 (4.1)	11,495 (1.4)	0.164	1,817 (4.0)	1,855 (4.1)	-0.004
Depression	10,603 (23.3)	324,387 (40.2)	-0.370	10,586 (23.3)	10,860 (23.9)	-0.014
Schizophrenia	5,687 (12.5)	56,550 (7.0)	0.185	5,676 (12.5)	5,998 (13.2)	-0.021
ACE-inhibitor	6,152 (13.5)	75,035 (9.3)	0.132	6,125 (13.5)	6,228 (13.7)	-0.007
Beta-blockers	5,786 (12.7)	76,471 (9.5)	0.103	5,753 (12.6)	5,857 (12.9)	-0.007
Oral anti-coagulants	1,025 (2.2)	9,540 (1.2)	0.082	993 (2.2)	981 (2.2)	0.002
Statins	6,787 (14.9)	91,915 (11.4)	0.104	6,762 (14.9)	6,928 (15.2)	-0.010

L2 Results

Stroke Risk for Antipsychotics (AP):
Overall, 1-15 days, 16-90 days, Haloperidol only

	Unmatched (site adjusted-only)				1:1 matched			
	# Exposed	Person years	# Events	HR (95% CI)	# Exposed	Person years	# Events	HR (95% CI)
Overall								
Typical AP	45,576	10,125.82	25	1.75 (1.17-2.63)	45,495	10,113.92	25	**0.87 (0.54-1.41)**
Atypical AP	806,611	338,987.22	396	1 (Ref)	45,495	20,646.19	53	1 (Ref)
1-15 days after exposure								
Typical AP	45,576	1,534.75	7	3.06 (1.37-6.83)	45,495	1,532.82	7	**1.16 (0.41-3.32)**
Atypical AP	806,611	32,431.81	42	1 (Ref)	45,495	1,829.06	7	1 (Ref)
16-90 days after exposure								
Typical AP	30,204	3,109.76	6	1.23 (0.54-2.80)	30,186	3,107.76	6	**0.52 (0.20-1.36)**
Atypical AP	757,812	96,228.27	124	1 (Ref)	30,186	3,885.00	14	1 (Ref)
Haloperidol only								
Haloperidol	13,882	3,369.51	9	1.80 (0.93-3.48)	13,841	3,366.33	9	**1.31 (0.54-3.21)**
Atypical AP	801,275	336,212.38	397	1 (Ref)	13,841	6,482.65	11	1 (Ref)

Survival Probability

Typica
Atypica

L2 Results:
Atypical APs + SSRI vs Z-Hypnotics + SSRI

Stroke Risk for Atypical Antipsychotics (APs) vs. z-hypnotics, adjusted for duration of SSRI use

	Unmatched (site-adjusted only)				1:1 matched			
	# Exposed	Person years	# Events	HR (95% CI)	# Exposed	Person years	# Events	HR (95% CI)
Overall								
Atypical AP + SSRI	303,428	121,662.27	147	0.89 (0.70-1.13)	214,453	85,129.30	112	**1.31 (0.93-1.84)**
Z-hyp + SSRI	516,456	131,308.61	144	1 (Ref)	214,453	52,090.92	49	1 (Ref)
1-15 days								
Atypical AP + SSRI	303,428	12,156.06	11	0.74 (0.35-1.56)	214,453	8,600.55	5	**0.71 (0.23-2.25)**
Z-hyp + SSRI	516,456	20,055.07	20	1 (Ref)	214,453	8,297.13	7	1 (Ref)
16-90 days								
Atypical AP + SSRI	286,586	36,596.09	45	0.88 (0.58-1.32)	192,817	24,316.00	32	**1.33 (0.76-2.33)**
Z-hyp + SSRI	438,894	43,234.33	51	1 (Ref)	192,817	19,349.82	20	1 (Ref)

Discussion

- No significant associations found in either analysis
  - Typical vs atypical APs: crude increased HR adjusted away with 1:1 propensity-score matching
  - Atypical vs z-hypnotics: modestly, but non-significant, increased HRs
  - Increased risk not ruled out completely
- Event rates low in non-elderly population
- 1:1 propensity-score matching reduced sample size and precision of estimates
  - Trade-off with improved confounding adjustment
- Did not assess subgroup risk by age group, dose

https://www.sentinelinitiative.org/sites/default/files/communications/publications-presentations/Sentinel-ICPE-2017-Symposium-Snapshot-of-the-First-Year_Antipsychotic_stroke.pdf

Regulatory Actions and Publications

- FDA decided that no action was necessary
  - Study results did not warrant labeling stroke risk for non-elderly/non-demented patients taking APs
- Presentation at the 2017 International Conference on Pharmacoepidemiology & Therapeutic Risk Management
- Taylor LG, Panucci G, Mosholder AD, Toh S, Huang TY, 2019. Antipsychotic Use and Stroke: A Retrospective Comparative Study in a Non-elderly Population. Journal of Clinical Psychiatry (*in press*).

https://www.sentinelinitiative.org/communications/publications/2017-icpe-symposium-integrating-sentinel-routine-regulatory-drug-review

For More Details …

Submit Comment

Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis

Project Title	**Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis**
Date Posted	*Thursday, November 2, 2017*
Project ID	cder_mpl2p_wp004
Status	Complete
Deliverables	Sentinel Modular Program Report: Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis, Report 1

For More Details …

Sentinel

Submit Comment

Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis

Project T

Date Pos

Project ID

Status

Deliverab

Submit Comment

Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis

Project Title	**Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis**
Date Posted	*Thursday, November 2, 2017*
Project ID	cder_mpl2p_wp005
Status	Complete
Deliverables	Sentinel Modular Program Report: Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis, Report 1

For More Details …

Sentinel

Sentinel

Sentinel Analytic Packages

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

Overview

A Sentinel analytic package is a standard folder structure containing detailed user-defined specifications, input files, SAS® macros, and SAS programs used to c
the user to select the cohort(s) of interest in order to examine their health profile and outcomes.

Sentinel's analytic request packages are intended to run on data formatted in accordance with the Sentinel Common Data Model (SCDM). Note that data must b

Analytic Request Packages Available for Download

Request ID	Summary
cder_mpl2r_wp008	Acute Myocardial Infarction and Hospitalized Heart Failure following Saxagliptin or Sitagliptin Use: a Propensity Score Matched Analysis
cder_mpl2p_wp009	Stroke, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Apixaban or Warfarin Use in Patients with Non-Valvular Atrial F
cder_mpl2p_wp006	Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis (an update to cder_mpl2p_wp002)
cder_mpl2p_wp005	Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a
cder_mpl2p_wp001	Venous Thromboembolism following Continuous or Extended Cycle Contraceptive Use: a Propensity Score Matched Analysis
cder_mpl2p_wp004	Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis

Questions?

info@sentinelsystem.org

Case Study 2: Biosimilars

Noelle M. Cocoros, DSc, MPH

Acknowledgements

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

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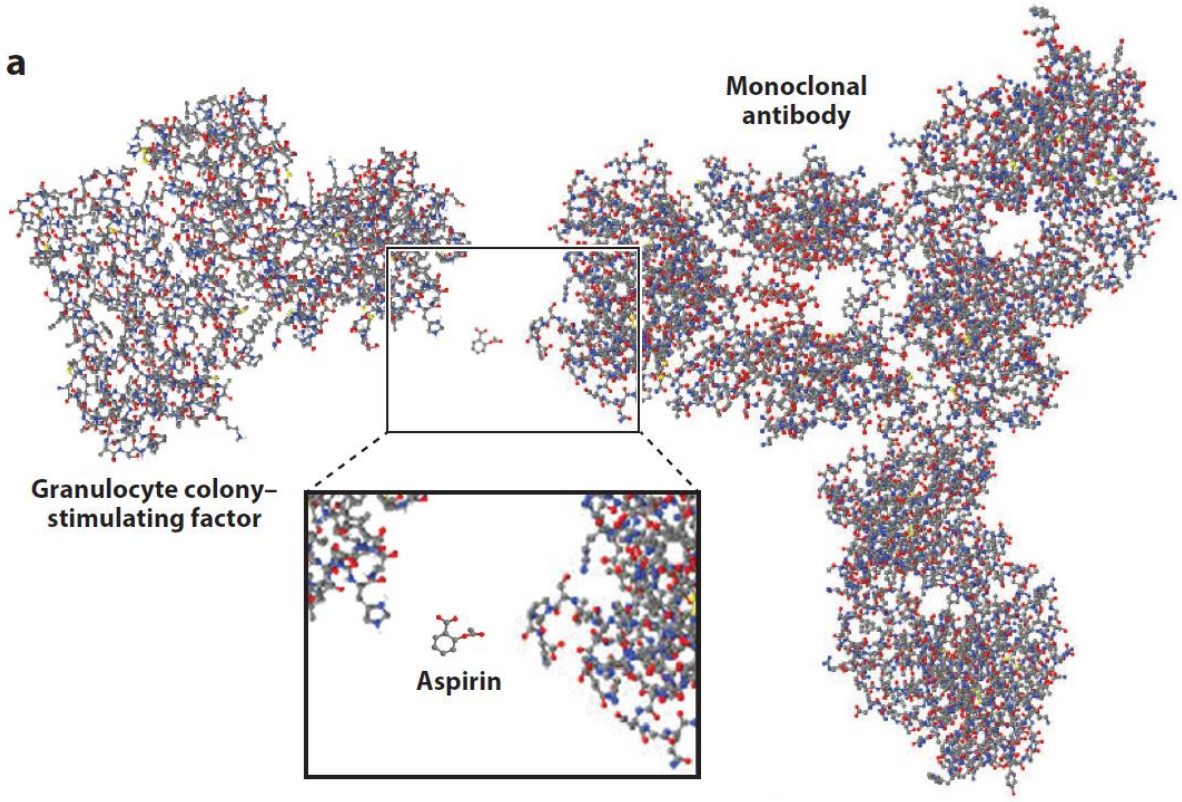
- Elizabeth Dee
- Sarah Dutcher
- Efe Eworuke
- Michael Nguyen

Many thanks are due to the Data Partners who provided the data used in these analyses

What is a Biologic?

- A "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings." *(PHS Act Section 351)*
- Generally derived from living organisms
- Significantly larger in size than small molecule drugs
- Complex in structure and often difficult to fully characterize



Christl LA, Woodcock J, Kozlowski S. Biosimilars: The US Regulatory Framework. Annu Rev Med. 2017 Jan 14;68:243-254.
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm

What is a Biosimilar?

- **Biosimilarity**: "…the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product" [PHS Act section 351(i)(2)]
- **Interchangeability**: "…may be **substituted** for the reference product **without the intervention of the health care provider** who prescribed the reference product" [PHS Act section 351(i)(3)]
  - "…for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of **alternating or switching** between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" [PHS Act section 351(k)(4)]

How Are Biosimilars Approved?

- Biologics Price Competition and Innovation (BPCI) Act of 2009 established a pathway to market biosimilars in the U.S.
- Stepwise approach that relies heavily on analytical methods to demonstrate through a "totality of the evidence" that a proposed product is biosimilar to its reference product
  - Integrates analytical, pharmacological, and clinical data
  - **Establishes safety and effectiveness through a demonstration of biosimilarity to the reference product**
  - Allows for the extrapolation of data across indications

Christl LA, Woodcock J, Kozlowski S. Biosimilars: The US Regulatory Framework. Annu Rev Med. 2017 Jan 14;68:243-54.

Why Study Biosimilars?

- Biologic products are complex molecules with inherent variability
  - Some lot-to-lot variation is expected due to their complex manufacturing processes
  - Two biological products can be determined to be structurally and functionally highly similar but are unlikely to be identical
  - Immunogenicity-related adverse events are a concern with product variability
- **Important to be able to monitor biosimilars after approval to evaluate potential safety concerns in the real-world**

Patel PK, King CR, Feldman SR. Biologics and biosimilars. J Dermatolog Treat. 2015;26(4):299-302.
Christl LA, Woodcock J, Kozlowski S. Biosimilars: The US Regulatory Framework. Annu Rev Med. 2017 Jan 14;68:243-254.

FDA Approved Biosimilars

(as of Dec. 31, 2018)

Reference Biologic	Biosimilar	Biosimilar Approval
Neupogen	Granix (tbo-filgrastim)*	8/29/2012
	Zarxio (filgrastim – sndz)	3/6/2015
	Nivestym (filgrastim – aafi)	7/20/2018
Remicade	Inflectra (infliximab – dyyb)	4/5/2016
	Renflexis (infliximab – abda)	4/21/2017
	Ixifi (infliximab – qbtx)	12/13/2017
Enbrel	Erelzi (etanercept – szzs)	8/30/2016
Humira	Amjevita (adalimumab – atto)	9/23/2016
	Cyltezo (adalimumab – adbm)	8/25/2017
	Hyrimoz (adalimumab – adaz)	10/30/2018
Avastin	Mvasi (bevacizumab – awwb)	9/14/2017
Herceptin	Ogivri (trastuzumab – dkst)	12/1/2017
	Herzuma (trastuzumab-pkrb)	12/14/2018
Epogen/Procrit	Retacrit (epoetin alfa – epbx)	5/15/2018
Neulasta	Fulphila (pegfilgrastim – jmdb)	6/4/2018
	Udenyca (pegfilgrastim – cbqv)	11/2/2018
Rituxan	Truxima (rituximab – abbs)	11/28/2018
No interchangeable products have been approved in the U.S.		

*Granix was approved prior to the abbreviated biosimilars pathway established in the BPCIA

Identifying Biosimilars

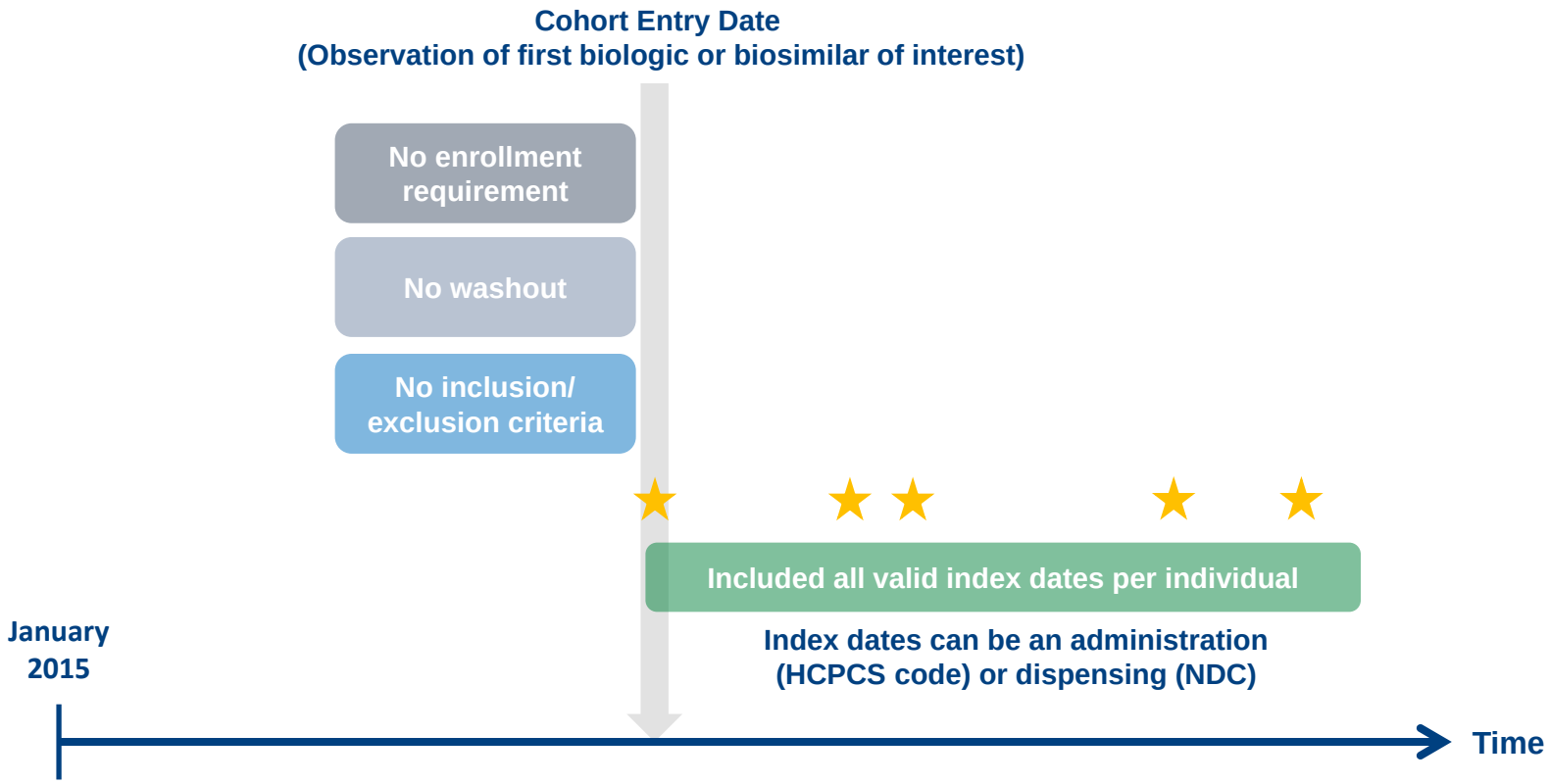
1. Proprietary names
2. Non-proprietary names
   - Biosimilars have a unique 4-letter suffix
3. Billing codes
   - Healthcare Common Procedure Coding System (HCPCS) procedure codes: drugs administered in a healthcare setting
     - Claims for **biosimilars** must include a 2-letter modifier that identifies the specific product manufacturer (until April 1, 2018)
   - National Drug Codes (NDC): outpatient pharmacy dispensings

Sentinel

Sentinel Exploratory Query

- Purpose: To describe how patients exposed to biologics and biosimilars are identified/captured using Sentinel's distributed database and Common Data Model
  - Are use of biologics and biosimilars identified in Sentinel with administrations in healthcare settings (HCPCS codes) or outpatient dispensings (NDCs)?
  - Can we observe uptake of biosimilars over time?
  - Are we potentially missing patients taking biosimilars in our data?
  - Are patients using infliximab biosimilars for different indications than the reference product?
  - Can the timing of observed biologic/biosimilar codes provide information about their use?

Identification of Billing Codes for Biosimilars



Claims Codes for Study Drugs

Non-proprietary Name	Proprietary Name	HCPCS Code – Modifier	9-Digit NDC
Filgrastim	Neupogen	J1442	55513-0209, 55513-0530, 55513-0546, 55513-0924, 54868-2522
Filgrastim-sndz	Zarxio	Q5101 – ZA	61314-0312, 61314-0304
Tbo-filgrastim	Granix	J1446, J1447	63459-0910, 63459-0912
Infliximab	Remicade	J1745	57894-0030
Infliximab-dyyb	Inflectra	Q5102 – ZB	00069-0809
Infliximab-abda	Renflexis	Q5102 – ZC	00006-4305
Unclassified Drugs		J3490	-
Unclassified Biologics		J3590	-

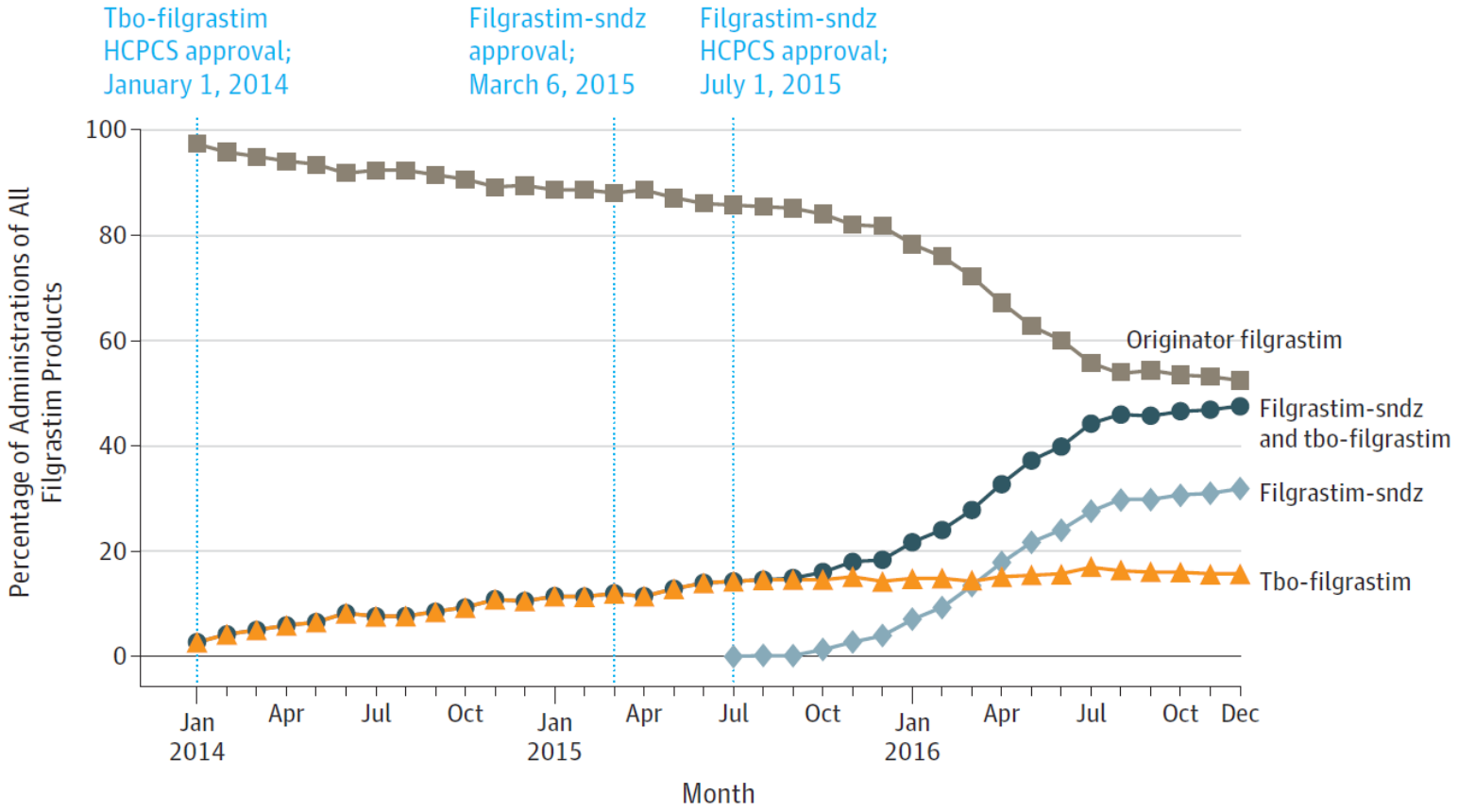
Filgrastim Biologics/Biosimilars Identified in Sentinel via Administrations and Dispensings

Biologic/ Biosimilar	Administrations (HCPCS)		Dispensings (NDC)	
	Patients	Mean Codes/Patient	Patients	Mean Dispensings/Patient
Neupogen	39,329	6.2	16,696	3.0
Zarxio	9,118	8.5	7,735	3.6
Granix	8,047*	4.9*	772	2.3
	5,165†	7.2†		

Filgrastim products are billed primarily using HCPCS codes, although some use is captured via dispensings

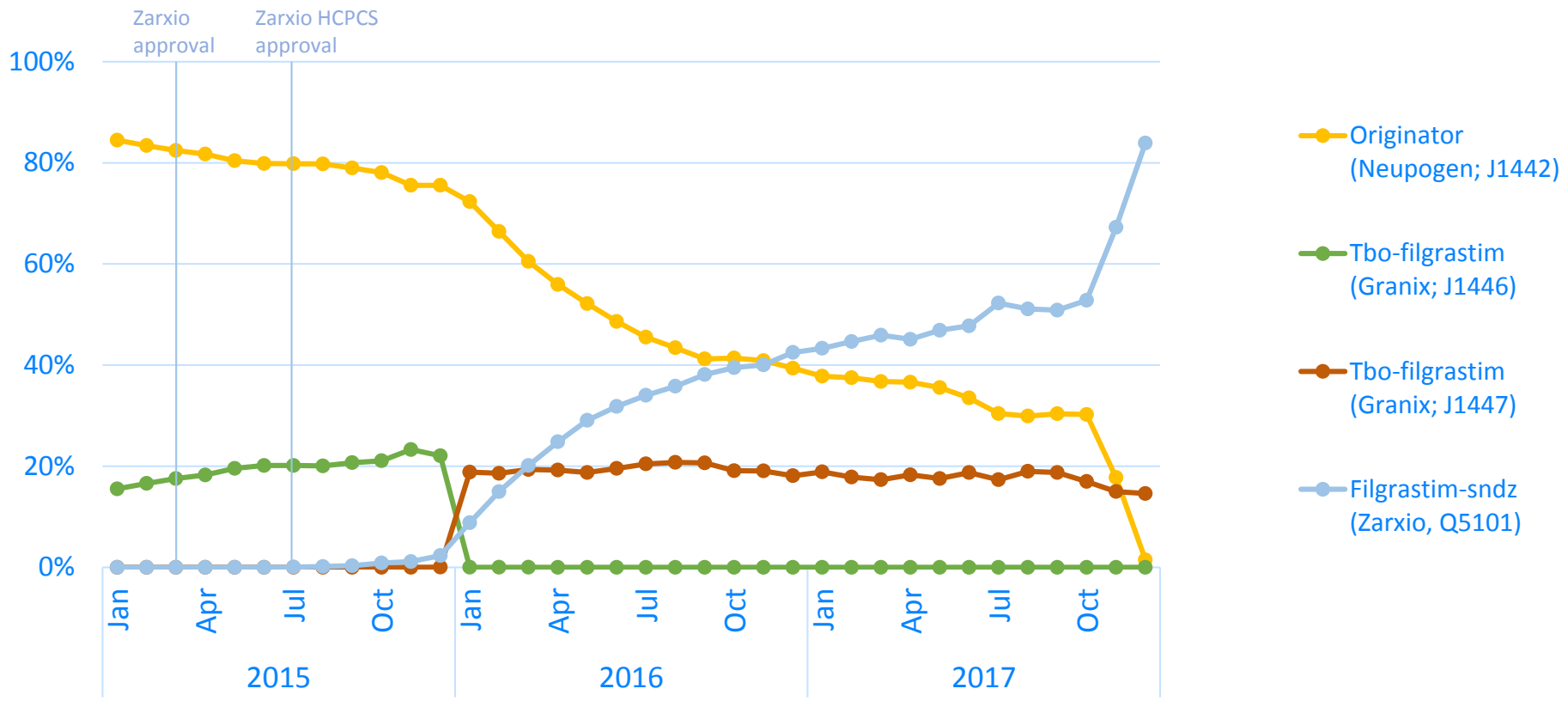
* HCPCS: J1446 † HCPCS: J1447

Proportion of Filgrastim Administrations Over Time in CMS



Kozlowski S et al. Uptake of the Biologic Filgrastim and Its Biosimilar Product Among the Medicare Population. JAMA. 2018;320(9):929-931.

Number and Proportion of Filgrastim Administrations Over Time in Sentinel



Infliximab Biologics/Biosimilars Identified in Sentinel via Administrations and Dispensings

Biologic/ Biosimilar	Administrations (HCPCS)		Dispensings (NDC)	
	Patients	Mean Codes/Patient	Patients	Mean Dispensings/Patient
Remicade	76,654	7.8	5,743	6.9
Inflectra	1,093*	2.5*	157	2.0
Renflexis			0	-

- There is low uptake of infliximab biosimilars
- Infliximab is billed primarily using HCPCs codes

* HCPCS: Q5102

Filgrastim Biologics/Biosimilars Identified in Sentinel via "Unclassified" Administrations

Biologic/ Biosimilar Dispensed	Patients with "Unclassified" HCPCS ±3 Days of a Dispensing		Patients with "Unclassified" HCPCS Same Day as Dispensing	
	J3490*	J3590†	J3490*	J3590†
Neupogen	496	5	232	1
Zarxio	172	0	101	0
Granix	35	0	15	0

There are few occurrences of filgrastim products potentially being billed using "unclassified" administration codes

* J3490: Unclassified drugs † J3590: Unclassified biologics

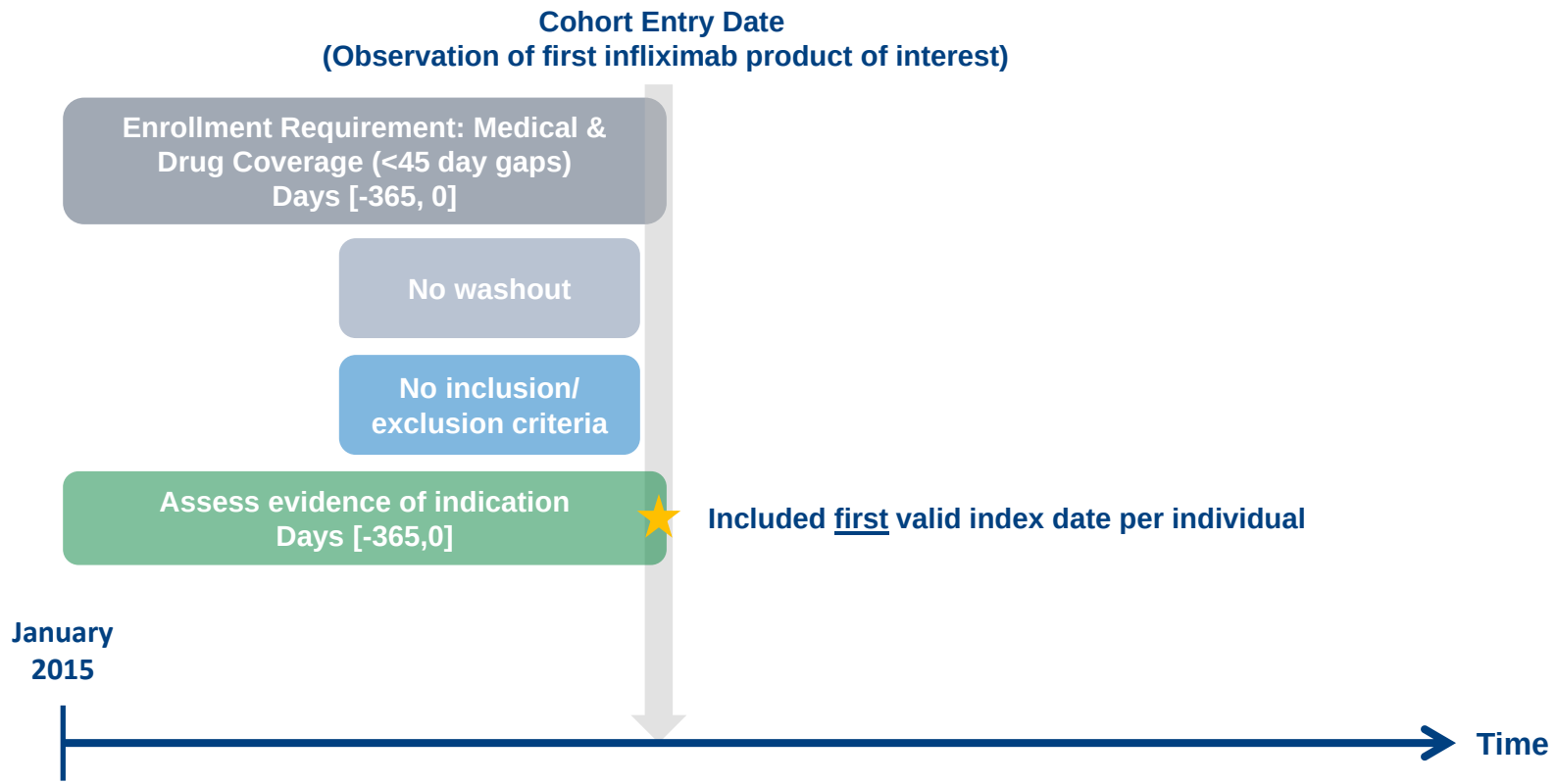
Infliximab Biologics/Biosimilars Identified in Sentinel via "Unclassified" Administrations

Biologic/ Biosimilar Dispensed	Patients with "Unclassified" HCPCS ±3 Days of a Dispensing		Patients with "Unclassified" HCPCS Same Day as Dispensing	
	J3490*	J3590†	J3490*	J3590†
Remicade	56	2	17	0
Renflexis	0	0	0	0
Inflectra	0	0	0	0

There are very few occurrences of infliximab products potentially being billed using "unclassified" administration codes

* J3490: Unclassified drugs † J3590: Unclassified biologics

Patient Characteristics for Infliximab Users



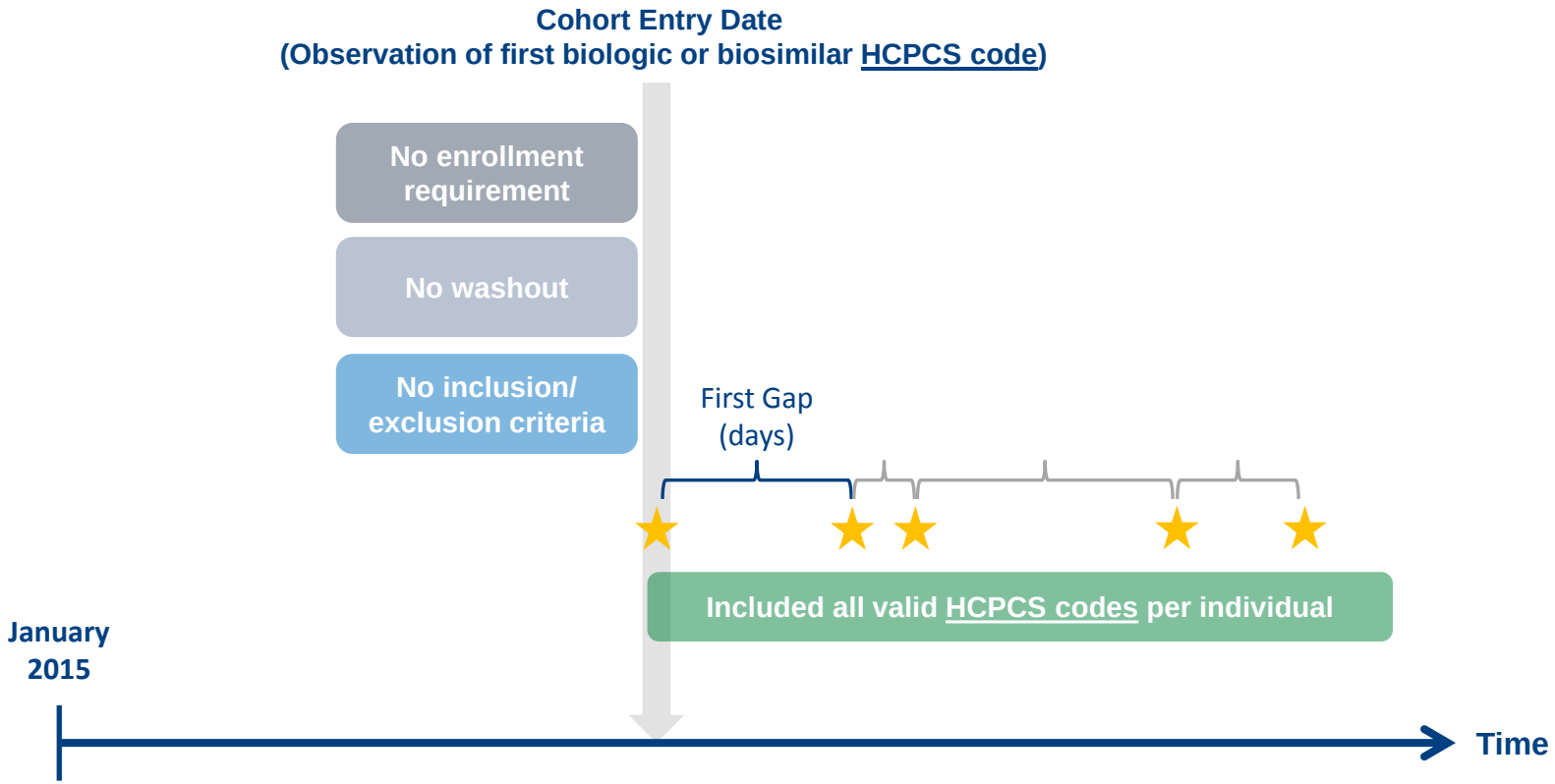
Patient Characteristics for Infliximab Users

	Remicade (N=64,487)	**Inflectra** (N=141)	**Renflexis** (N=0)
Age, years (mean, SD)	52.2 (16.4)	59.1 (15.6)	-
Female (%)	59.8	63.1	-
Year (%)			
2015	73.7	0	-
2016	15.2	0	-
2017	11.1	100	-
Recorded history in the 365 days prior to drug use (%)			
GI conditions*	51.3	13.5	-
Non-GI conditions†	51.6	80.1	-
Neither	2.8	9.2	-

* Ulcerative colitis, Crohn's disease

† Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, Psoriasis

Gaps Between Administrations



Gap Between Filgrastim Administrations

	Total # Administrations	# Patients with >1 Admin.	First Gap (days)		
			Median	IQR	Mean (SD)
Neupogen	134,387	18,917	12	4-26	25.1 (50.1)
Zarxio	35,316	5,136	11	3-20	19.8 (36.9)
Granix	19,201	2,617	11	4-22	22.8 (45.9)

Among those with >1 filgrastim administration, the median gap between the first and second administration was 11-12 days

- This did not differ between the reference biologic and biosimilars

Gap Between Infliximab Administrations

	Total # Administrations	# Patients with >1 Admin.	First Gap (days)		
			Median	IQR	Mean (SD)
Remicade	554,530	64,430	48	27-55	46.6 (41.5)
Infliximab biosimilar*	2,852	698	41	17-55	42.3 (24.3)

Among those with >1 infliximab administration, the median gap between the first and second administration was 41-48 days

*Inflximab biosimilar: Q5102 (Renflexis or Inflectra)

Summary

- Filgrastim and infliximab are billed primarily as administrations in healthcare encounters (HCPCS codes)
  - Substantial use is billed via dispensings (NDCs)
  - Rarely billed using “unclassified” administrations
- Data on observed gaps may reflect use patterns
  - Can be used when creating exposure definitions in future analyses
- Sentinel Distributed Data Network and Common Data Model can be used for surveillance of biologics and biosimilars
- Sentinel’s analytic tools have numerous capabilities

Questions?

info@sentinelsystem.org

Case Study 3: Duration of Follow-Up for Chronic Condition Cohorts in the Sentinel System

Mayura Shinde, DrPH, MPH
Sentinel Operations Center
04/04/2019

Acknowledgements

DEPARTMENT OF POPULATION MEDICINE

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- Andrew Petrone
- Libby Dee
- Sarah Dutcher
- Michael Nguyen

Many thanks are due to the Data Partners who provided the data used in these analyses

Outline

- Background
- Study Objective
- Chronic Conditions Warehouse (CCW) Algorithm
- Steps for Adaptation of CCW in Sentinel
- Results
- Limitations
- Summary

Background

- Ability to assess outcomes in Sentinel relies on sufficient observation time
- Median length of observation time for individuals in large commercial insurance claims databases is approximately <2 years[1]
- It is unknown if individuals with specific chronic conditions have substantially different follow-up time
  - Having consistent health insurance may be more important to those who engage the health care system more regularly

[1] Jensen ET, Cook SF, Allen JK, et al. Enrollment factors and bias of disease prevalence estimates in administrative claims data. Ann Epidemiol. 2015;25(7):519-525.

Study Objective

- To identify and describe individuals with chronic conditions in Sentinel
  - Estimate chronic condition cohort sample size
  - Assess duration of follow up for each chronic condition cohort

Chronic Conditions Data Warehouse

Your source for national CMS Medicare and Medicaid research data

Search... Search

Home | Medicare Data | Medicaid Data | Data Dictionaries | Condition Categories | Analytic Guidance | Pricing

Chronic Conditions Data Warehouse » About CCW

About Chronic Condition Data Warehouse

The Centers for Medicare & Medicaid Services (CMS) launched the Chronic Conditions Data Warehouse (CCW), a research database, in response to the Medicare Modernization Act of 2003 (MMA). Section 723 of the MMA outlined a plan to improve the quality of care and reduce the cost of care for chronically ill Medicare beneficiaries. In addition to chronic conditions, the CCW supports health policy analysis and other CMS initiatives.

Introduction to CCW: View this Chronic Conditions Data Warehouse informational video to learn how you can access, analyze, and aggregate all the data you need like never before!

The Beneficiary Link

The CCW data are linked by a unique, unidentifiable beneficiary key, which allows researchers to analyze information across the continuum of care.

The CCW is designed to:

https://www.ccwdata.org/web/guest/about-ccw

Chronic Conditions Data Warehouse

Your source for national CMS Medicare and Medicaid research data

Search... Search

Home | Medicare Data | Medicaid Data | Data Dictionaries | Condition Categories | Analytic Guidance | Pricing

Chronic Conditions Data Warehouse » A

About Chronic Conditi

The Centers for Medicare & Medicaid
Modernization Act of 2003 (MMA). Se
addition to chronic conditions, the CC

Introduction to CCW: View t
never before!

The Beneficiary Link

The CCW data are linked by a unique

The CCW is designed to:

Chronic Conditions Data Warehouse » Condition Categories

Condition Categories

The CCW includes variables for 66 conditions – 27 common chronic conditions and 39 other chronic or potentially disabling conditions, which identify additional chronic health, mental health and substance abuse conditions. These variables are developed to facilitate researchers in the identification of cohorts of beneficiaries with specific conditions. Researchers may request data for a specific predefined cohort based on any of the categories on this page.

The condition variables are developed from algorithms that search the CMS administrative claims data for specific diagnosis codes, MS-DRG codes, or procedure codes. On October 1, 2015 the conversion from the 9th version of the International Classification of Diseases to version 10 occurred. Regardless of when a claim was submitted for payment, services that occurred prior to October 1, 2015, use ICD-9 codes.

All of the variables listed on this page are currently available in the **Master Beneficiary Summary File (MBSF)**, **Medicare-Medicaid Linked Enrollee Analytic Data Source (MMLEADS)** and **Medicaid Enrollee Supplemental File (MESF)**.

CCW Chronic Conditions

There are 27 chronic condition categories, available for file years 1999 - forward.

- CCW Chronic Condition Algorithms
- CCW Chronic Condition Algorithms Reference List

Original Version - 21 CCW Chronic Conditions for file years 1999-2010

This original version is no longer available, but listed here for reference purposes

CCW Chronic Conditions	
Acquired Hypothyroidism	Chronic Kidney Disease
Acute Myocardial Infarction	Chronic Obstructive Pulmonary Disease
Alzheimer's Disease	Depression
Alzheimer's Disease, Related Disorders, or Senile Dementia	Diabetes
Anemia	Glaucoma
Asthma	Heart Failure
Atrial Fibrillation	Hip / Pelvic Fracture

https://www.ccwdata.org/web/guest/about-ccw

CCW Chronic Conditions

- Acquired Hypothyroidism
- Acute Myocardial Infarction
- *Alzheimer's Disease*
- Alzheimer's Disease, Related Disorders, or Senile Dementia
- Anemia
- Asthma
- Atrial Fibrillation
- Benign Prostatic Hyperplasia
- Cancer: Colorectal
- Cancer: Endometrial
- Cancer: Breast
- Cancer: Lung
- Cancer: Prostate
- *Cataract*
- Chronic Kidney Disease
- Chronic Obstructive Pulmonary Disease
- Depression
- Diabetes
- Glaucoma
- Heart Failure
- *Hip/Pelvic Fracture*
- Hyperlipidemia
- Hypertension
- Ischemic Heart Disease
- Osteoporosis
- Rheumatoid Arthritis/ Osteoarthritis
- Stroke/Transient Ischemic Attack

CMS Chronic Conditions Data Warehouse (CCW)

CCW Condition Algorithms

(rev. 06/2018)

Algorithms	Reference Period (# of years)	Valid ICD-9 / CPT4 / HCPCS Codes[1]	Valid ICD-10 / CPT4 / HCPCS Codes[1]	Number / Type of Claims to Qualify[2]
Asthma	1 year	DX 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92, **(any DX on the claim)**	DX J45.20, J45.21, J45.22, J45.30, J45.31, J45.32, J45.40, J45.41, J45.42, J45.50, J45.51, J45.52, J45.901, J45.902, J45.909, J45.990, J45.991, J45.998 **(any DX on the claim)**	At least 1 inpatient, SNF, HHA ***OR*** 2 HOP or Carrier claims with DX codes
Atrial Fibrillation	1 year	DX 427.31 **(ONLY first or second DX on the claim)**	DX I48.0, I48.1, I48.2, I48.91 **(ONLY first or second DX on the claim)**	At least 1 inpatient ***OR*** 2 HOP or Carrier claims with DX codes
Benign Prostatic Hyperplasia	1 year	DX 600.00, 600.01, 600.10, 600.11, 600.20, 600.21, 600.3, 600.90, 600.91 **(any DX on the claim)** ***EXCLUSION:*** *If any of the qualifying claims also have an ICD-9 diagnosis of 222.2, then EXCLUDE*	DX N40.0, N40.1, N40.2, N40.3, N42.83 **(any DX on the claim)** ***EXCLUSION:*** *If any of the qualifying claims also have an ICD - 10 diagnosis of D29.1, then EXCLUDE*	At least 1 inpatient, SNF, HHA ***OR*** 2 HOP or Carrier claims with DX codes

https://www.ccwdata.org/web/guest/condition-categories

CCW Algorithm Mapping

CCW Claim Type	Primary DX position required	Secondary DX position required	Any DX is allowed
Inpatient	IPP	ISS	IP*
Skilled nursing facility (SNF)	ISP	ISS	IS*
Home health agency (HHA)	–	–	–
Hospital outpatient (HOP)	AV*, OA*, ED*	AV*, OA*, ED*	AV*, OA*, ED*
Carrier	AV*, OA*, ED*	AV*, OA*, ED*	AV*, OA*, ED*

IP = Inpatient; IS = Institutional Stay (IS); AV = Ambulatory Visit; OA = Other Ambulatory; ED = Emergency
P = primary; S = secondary; * = any diagnosis position

Since DPs are not required to report a primary or secondary discharge dx for AV, OA, or ED encounters, algorithms requiring a primary or secondary diagnosis were modified to include diagnoses from *any position* for AV, OA, or ED encounters

CCW Reference Period

- CCW algorithms list a reference period for each condition (range 1-3 years)
  - In our analysis, we applied these as an lookback period, enrollment requirement, and washout period for qualifying claims

Query Cohort	Lookback Period[1]	Enrollment Requirement	Washout Period[2]
Prevalent	CCW reference period	0	0
Incident	CCW reference period	CCW reference period	CCW reference period
Incident (sensitivity)	1 year	1 year	1 year

[1]Period during which qualifying inclusion claims were required to occur, when 2 AV/OA/ED claims were required
[2]Period with no evidence of claims for a chronic condition, for identification of incident diagnosis
AV = Ambulatory Visit; OA = Other Ambulatory; ED = Emergency

Hypertension Algorithm Example

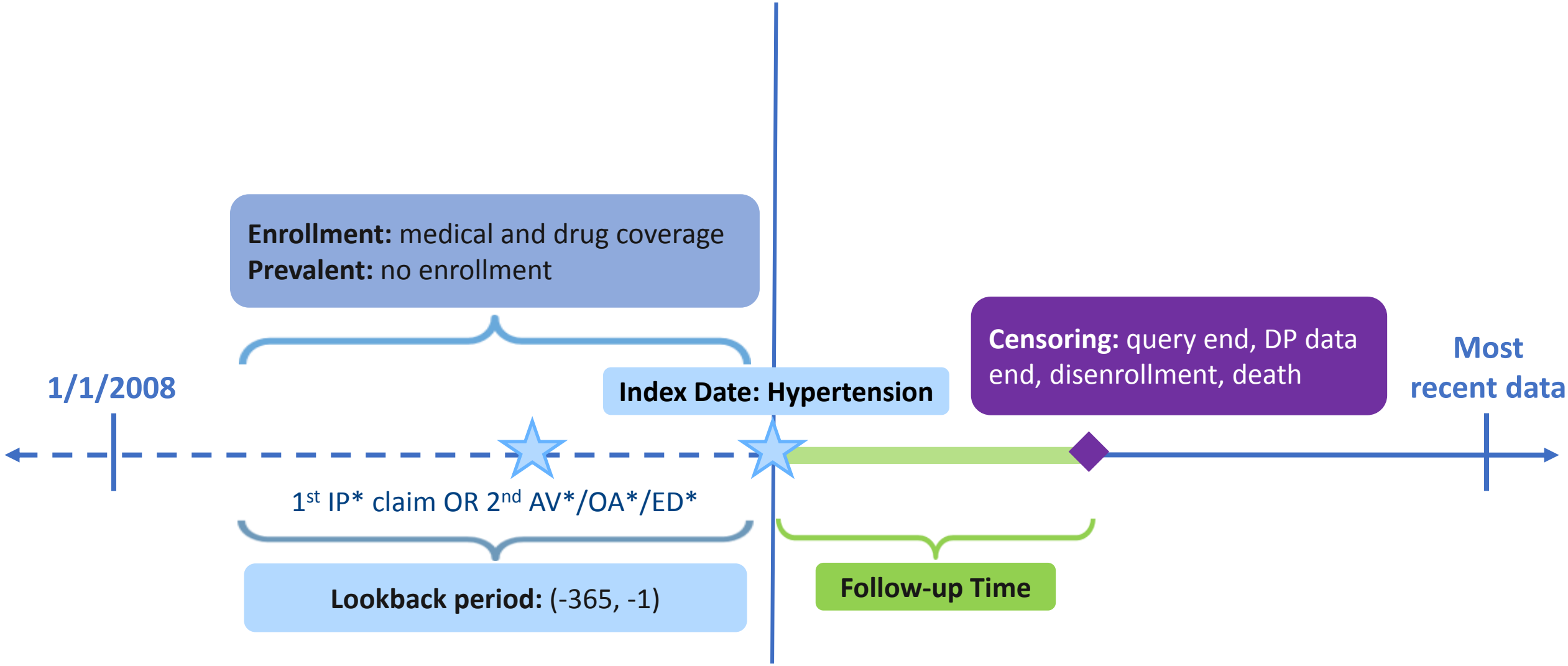
CMS Chronic Conditions Data Warehouse (CCW)

CCW Condition Algorithms

(rev. 06/2018)

Algorithms	Reference Period (# of years)	Valid ICD-9 / CPT4 / HCPCS Codes[1]	Valid ICD-10 / CPT4 / HCPCS Codes[1]	Number / Type of Claims to Qualify[2]	Number / Type of Claims to Qualify[2]
Hypertension	1 year	DX 362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2 **(any DX on the claim)**	DX H35.031, H35.032, H35.033, H35.039, I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I15.9, I67.4, N26.2 **(any DX on the claim)**	At least 1 inpatient, SNF, HHA ***OR*** 2 HOP or Carrier claims with DX codes	At least 1 inpatient, SNF, HHA ***OR*** 2 HOP or Carrier claims with DX codes

Hypertension Algorithm – Prevalent Cohort



CCW Reference Period

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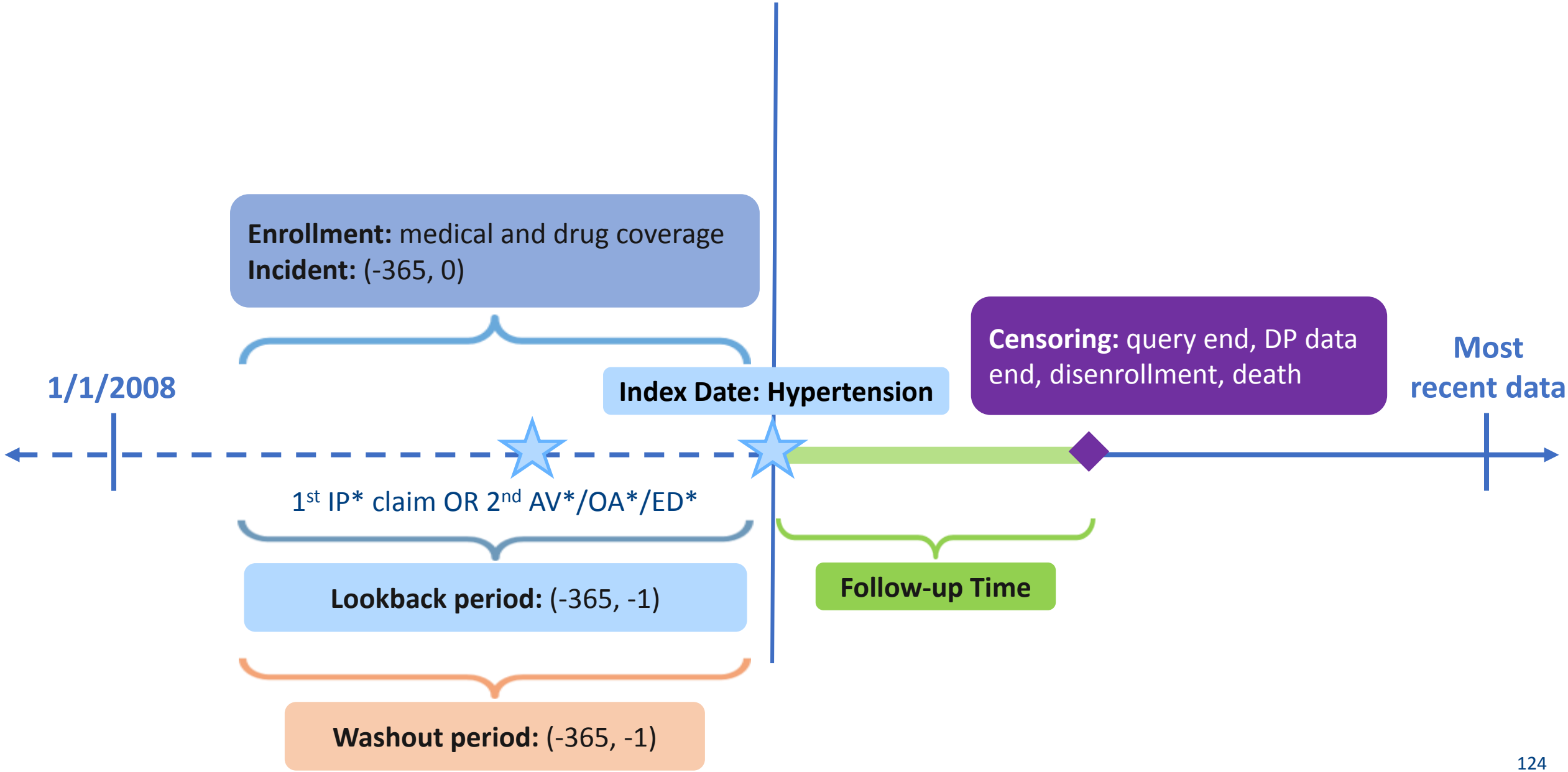
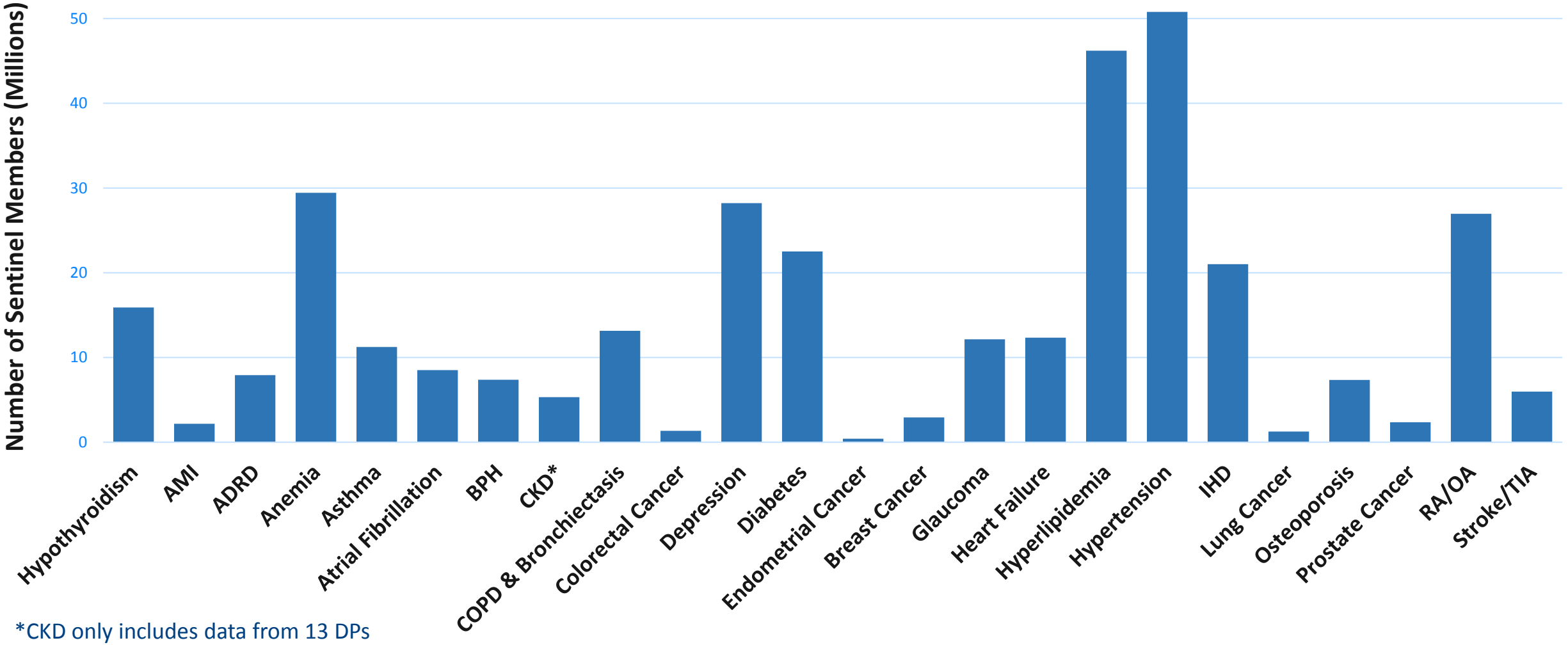
Query Cohort	Lookback Period[1]	Enrollment Requirement	Washout Period[2]
Prevalent	CCW reference period	0	0
Incident	CCW reference period	CCW reference period	CCW reference period
Incident (sensitivity)	1 year	1 year	1 year

[1]Period during which qualifying inclusion claims were required to occur, when 2 AV/OA/ED claims were required
[2]Period with no evidence of claims for a chronic condition, for identification of incident diagnosis
AV = Ambulatory Visit; OA = Other Ambulatory; ED = Emergency

Hypertension Algorithm – Incident Cohort



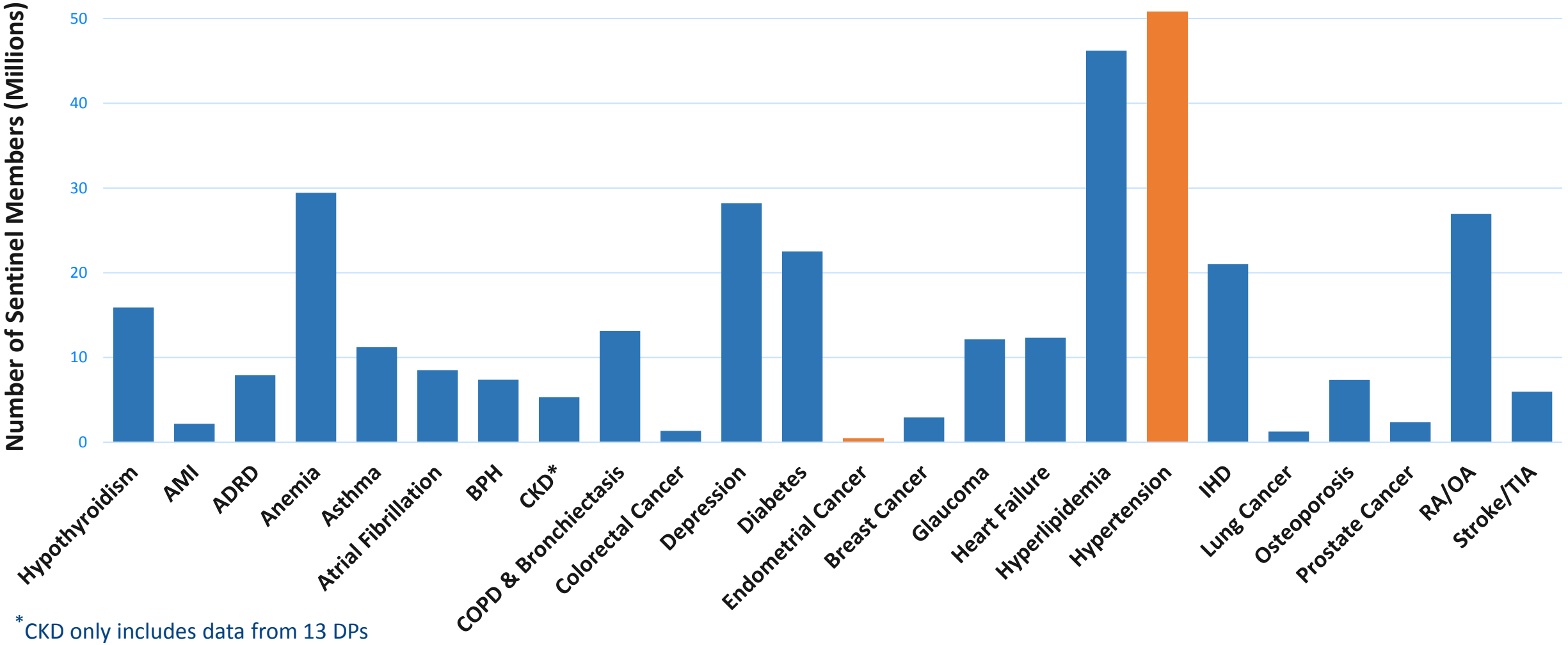
Members with Prevalent CCW Chronic Conditions



*CKD only includes data from 13 DPs

AMI: Acute Myocardial Infarction; ADRD: Alzheimer's Disease & Related Disorders; BPH: Benign Prostatic Hyperplasia; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; IHD: Ischemic Heart Disease; RA/OA: Rheumatoid Arthritis/Osteoarthritis; TIA: Transient Ischemic Attack

Members with Prevalent CCW Chronic Conditions



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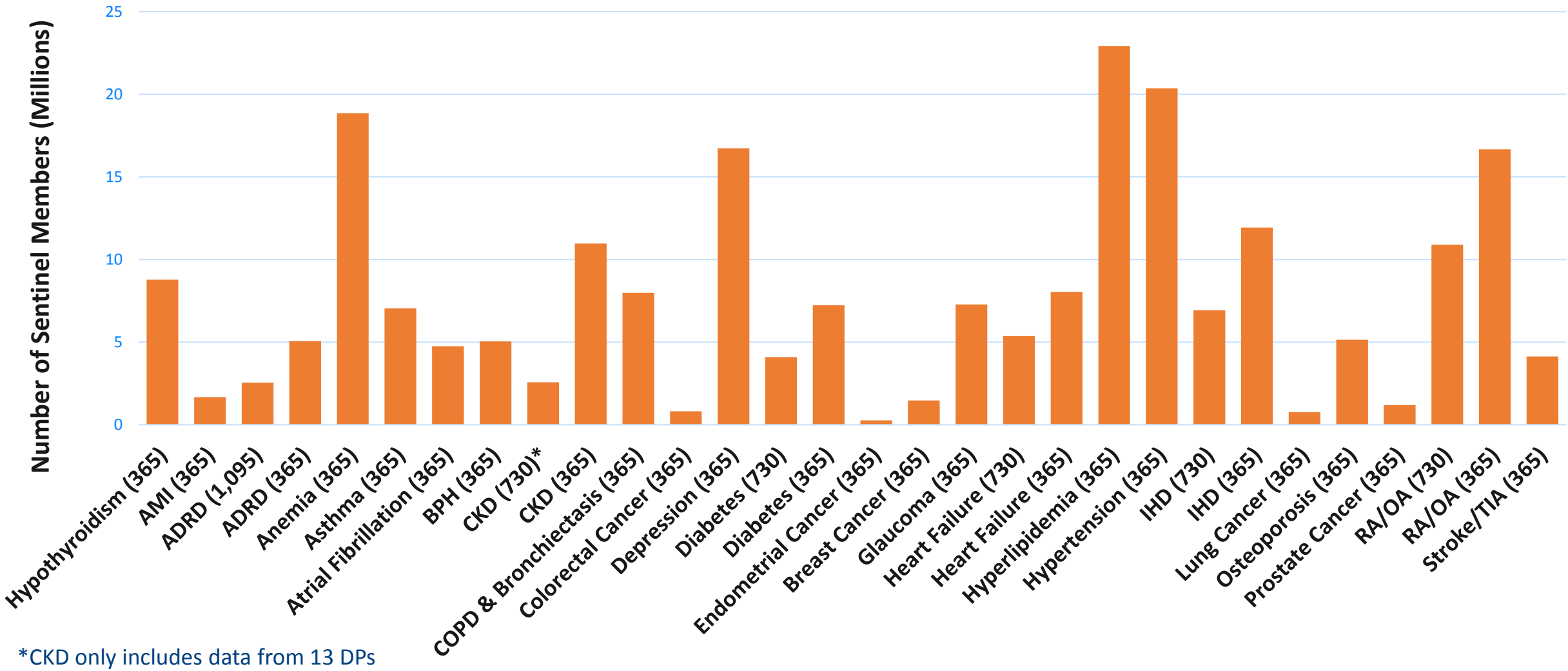
Members with Incident CCW Chronic Conditions

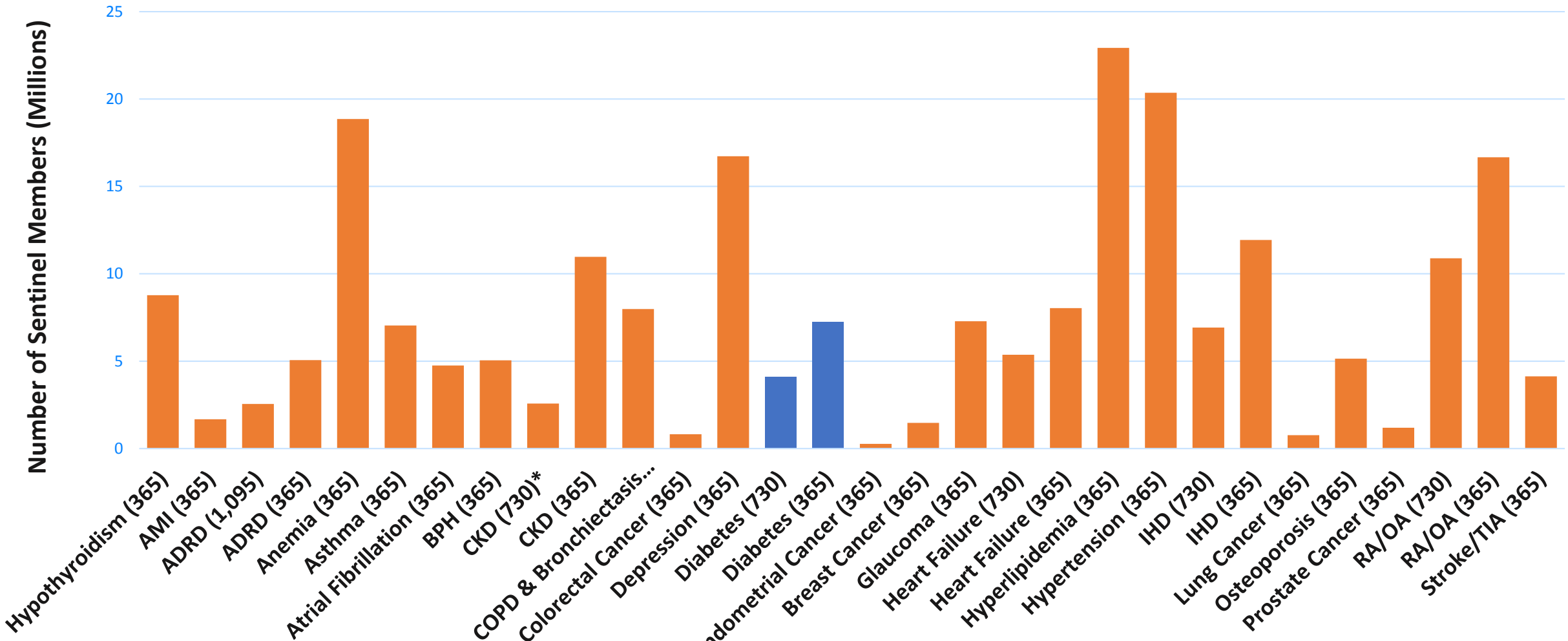


*CKD only includes data from 13 DPs

Number in parentheses represents the washout period in days

AMI: Acute Myocardial Infarction; ADRD: Alzheimer's Disease & Related Disorders; BPH: Benign Prostatic Hyperplasia; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; IHD: Ischemic Heart Disease; RA/OA: Rheumatoid Arthritis/Osteoarthritis; TIA: Transient Ischemic Attack

Members with Incident CCW Chronic Conditions



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AMI: Acute Myocardial Infarction; ADRD: Alzheimer's Disease & Related Disorders; BPH: Benign Prostatic Hyperplasia; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; IHD: Ischemic Heart Disease; RA/OA: Rheumatoid Arthritis/Osteoarthritis; TIA: Transient Ischemic Attack

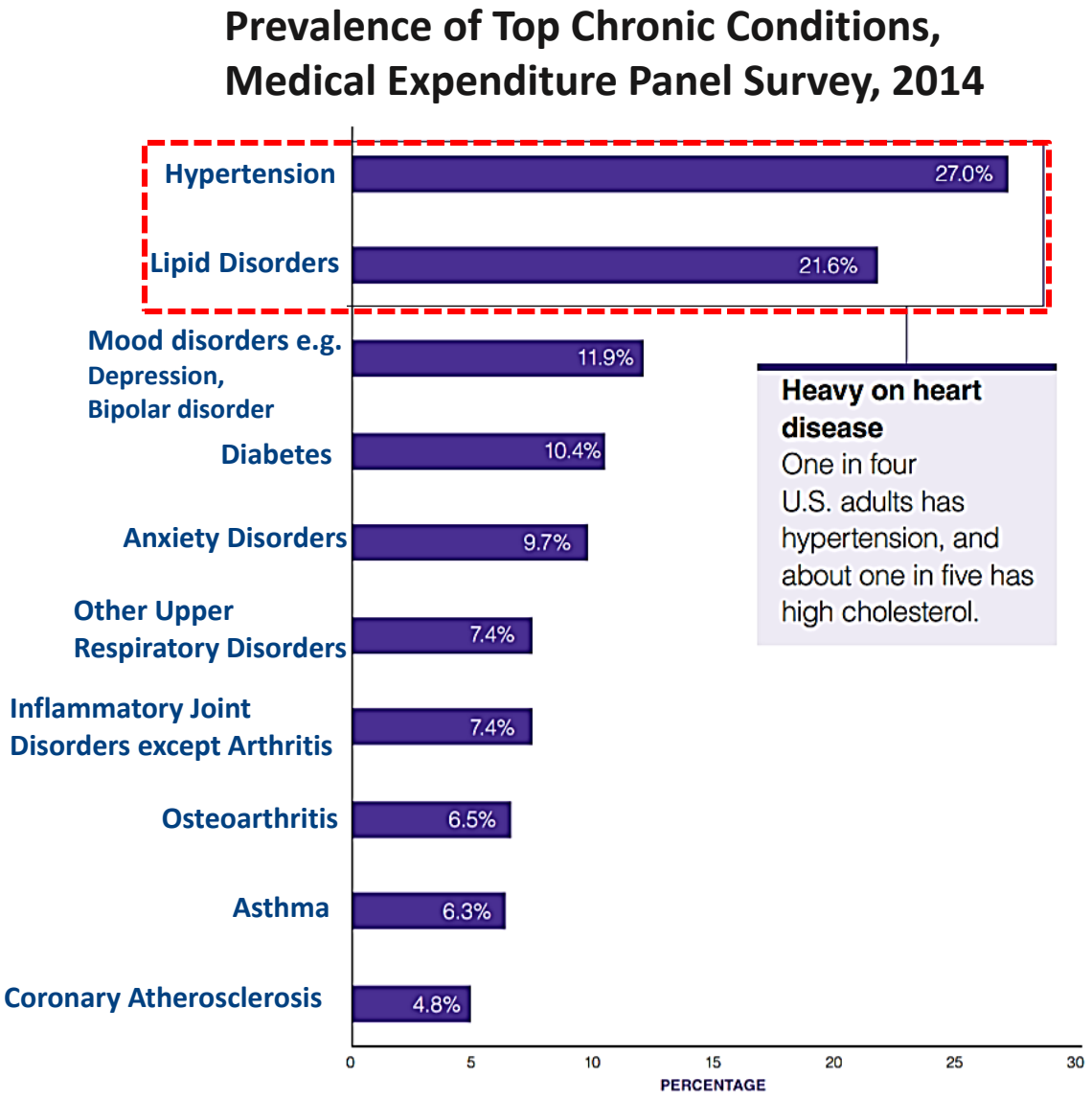
Chronic Condition Prevalence Comparison

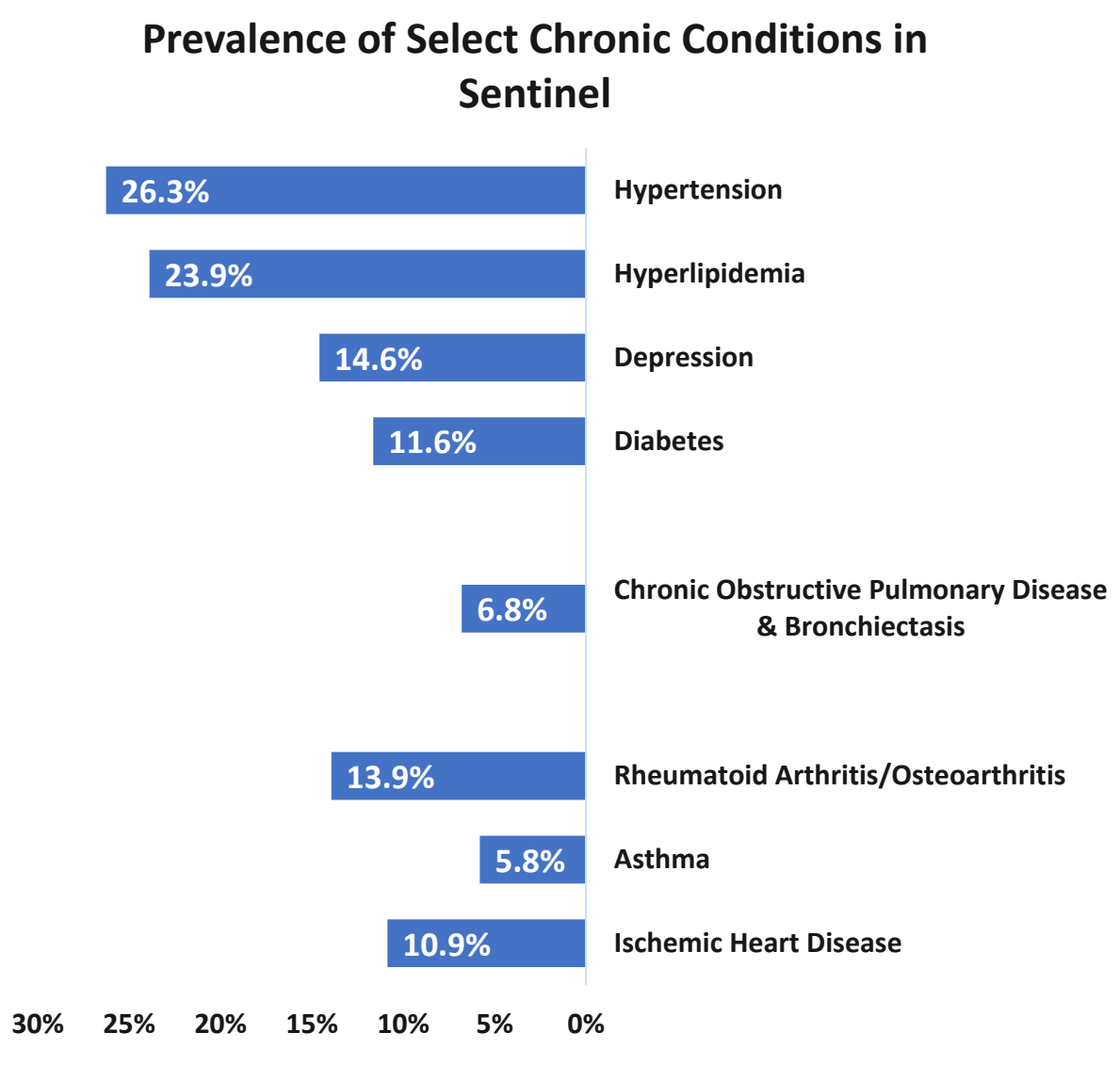
	Self reported NCHS/CDC[1,2]	Sentinel
Asthma	8.3%	5.8%
Arthritis	21.6%	13.9%
Breast cancer	1.5%	1.5%
Chronic Kidney Disease	1.9%	4.5%
Diabetes	8.8%	11.6%
Hypertension	24.9%	26.3%
Ischemic Heart Disease	5.7%	10.9%
Prostate cancer	2.2%	1.2%
Stroke	2.8%	3.4%

[1] Blackwell DL, Villarroel MA. Tables of Summary Health Statistics for U.S. Adults: 2016 National Health Interview Survey. National Center for Health Statistics. 2018. Available from: http://www.cdc.gov/nchs/nhis/SHS/tables.htm

[2] Prevalence among adults 18 years and older

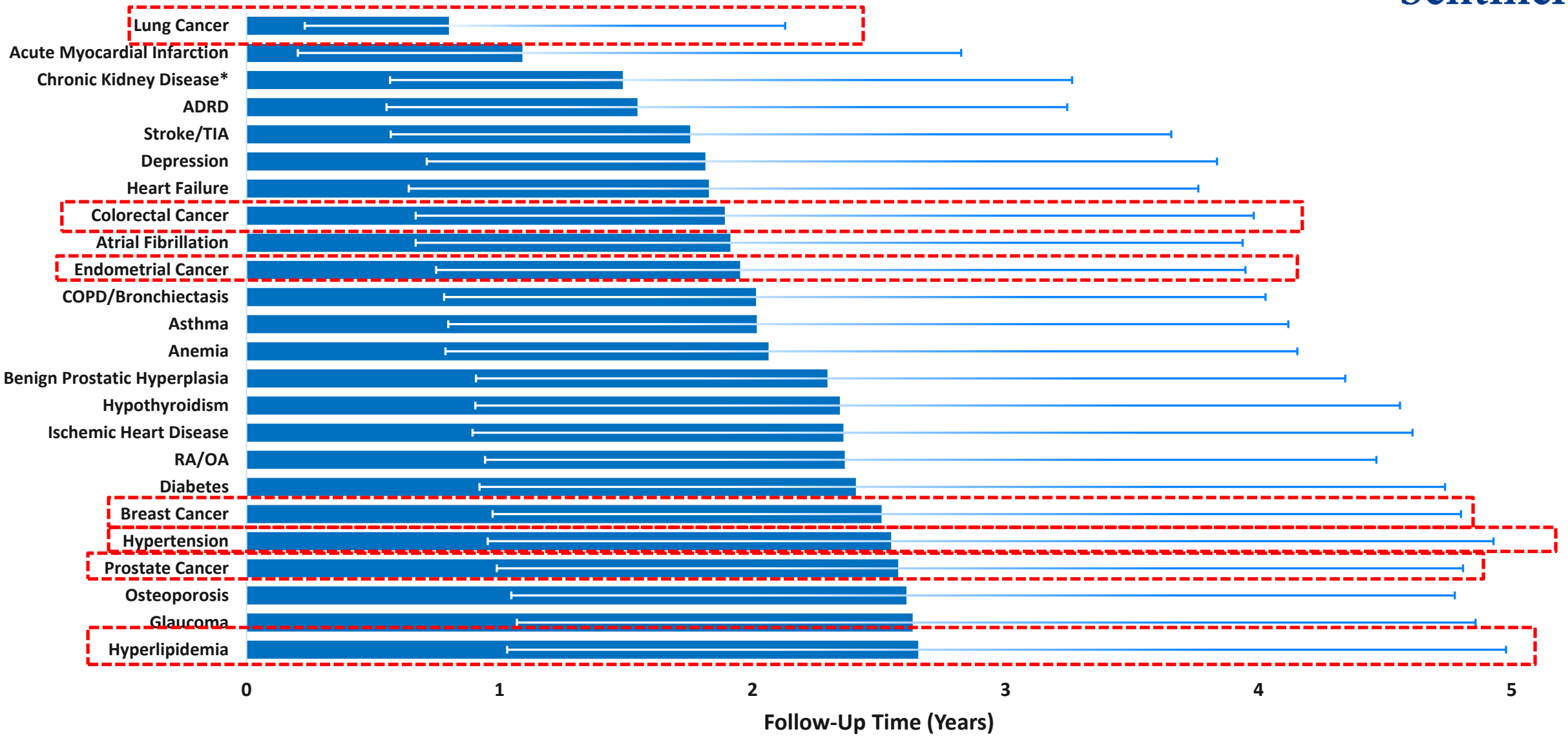
Chronic Condition Prevalence Comparison





Multiple Chronic Conditions in the United States, Christine Buttorff et al., RAND Corporation, TL-221-PFCD, 2017. Available at: www.rand.org/t/TL221

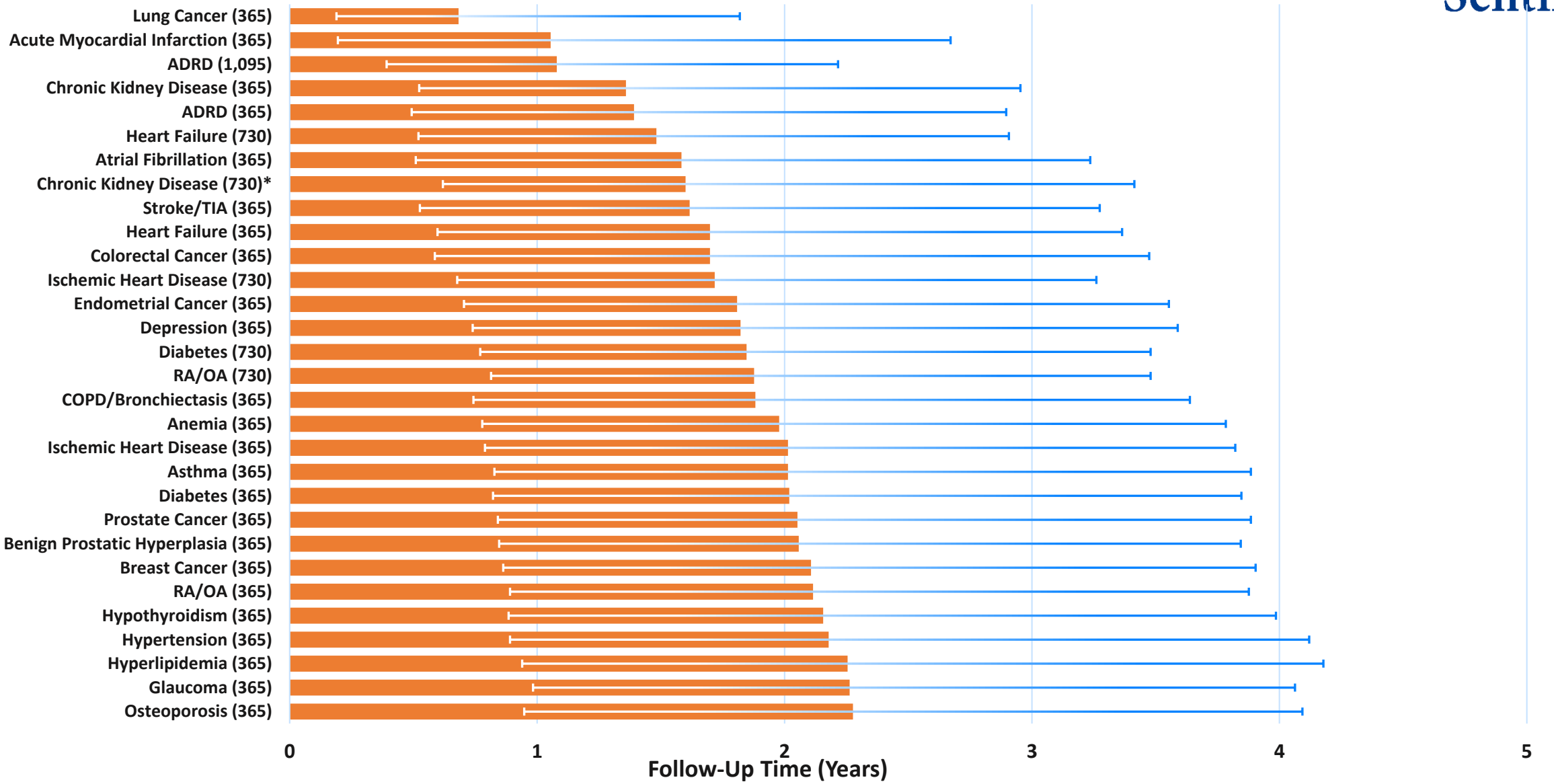
Median Inter-Quartile Length of Follow Up Time, By Prevalent Chronic Condition



*CKD only includes data from 13 DPs

ADRD: Alzheimer's Disease & Related Disorders; COPD: Chronic Obstructive Pulmonary Disease;
RA/OA: Rheumatoid Arthritis/Osteoarthritis; TIA: Transient Ischemic Attack

Median Inter-Quartile Range Length of Follow Up Time, By Incident Chronic Condition

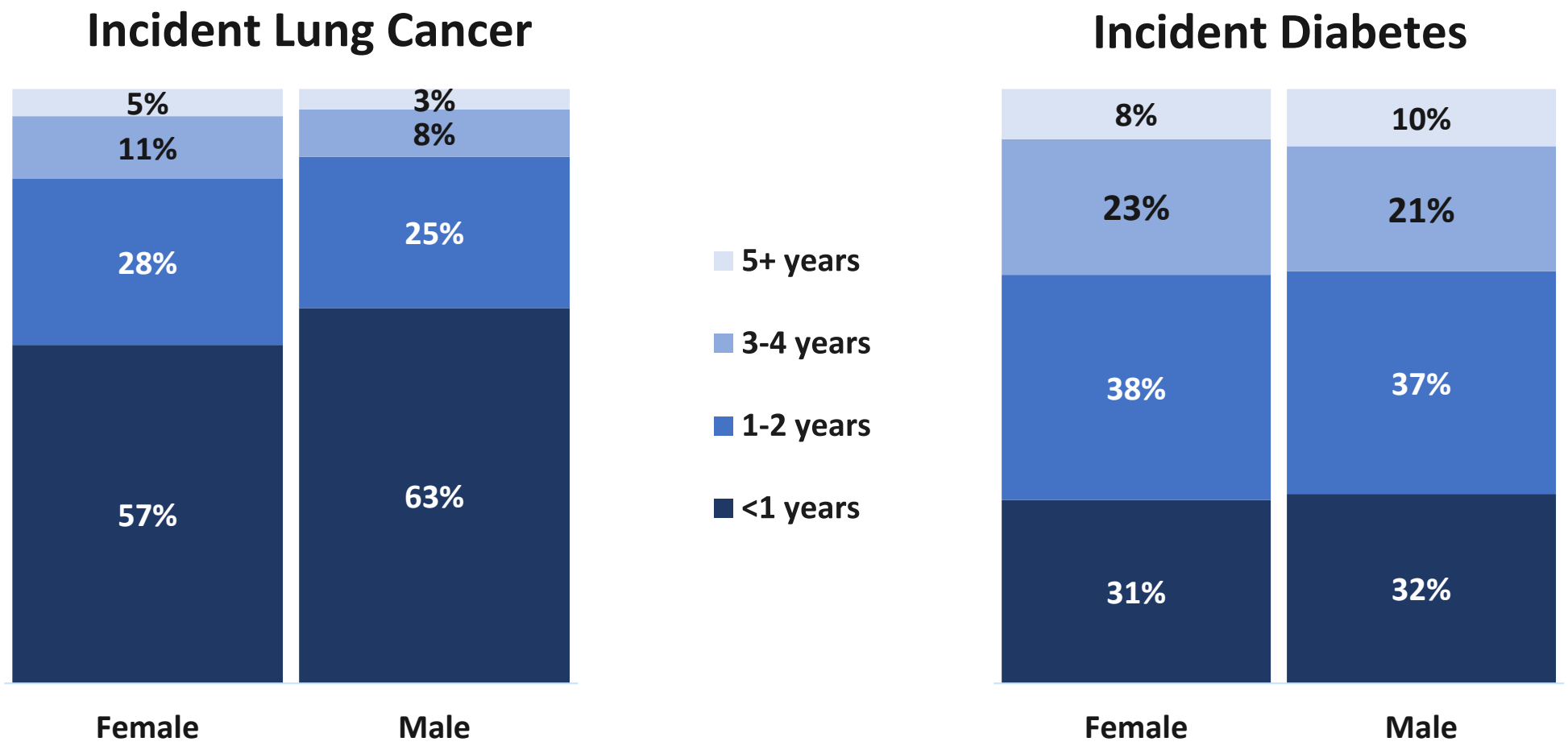


*CKD only includes data from 13 DPs; 365/730/1095 corresponds to washout and enrollment criteria applied for identifying the incident condition

ADRD: Alzheimer's Disease & Related Disorders; COPD: Chronic Obstructive Pulmonary Disease;
RA/OA: Rheumatoid Arthritis/Osteoarthritis; TIA: Transient Ischemic Attack

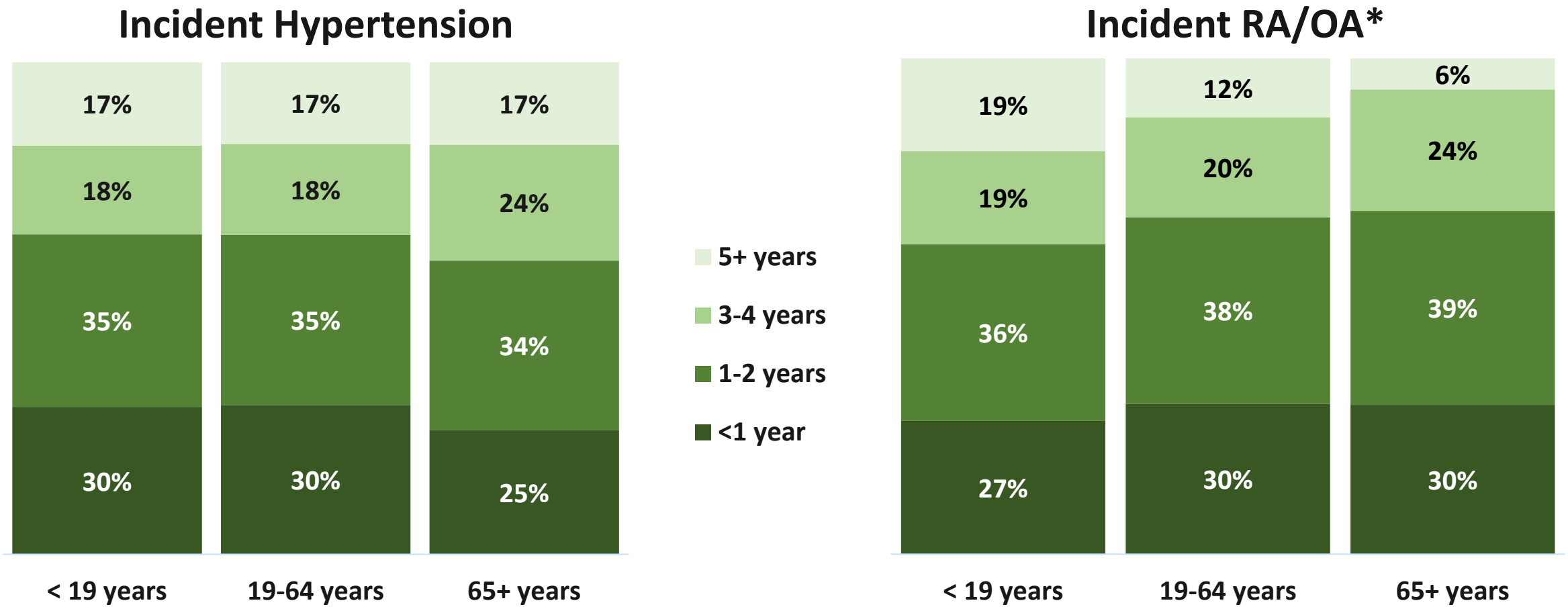
Follow-Up Time by Sex

- Follow-up time is similar across males and females



Follow-Up Time by Age

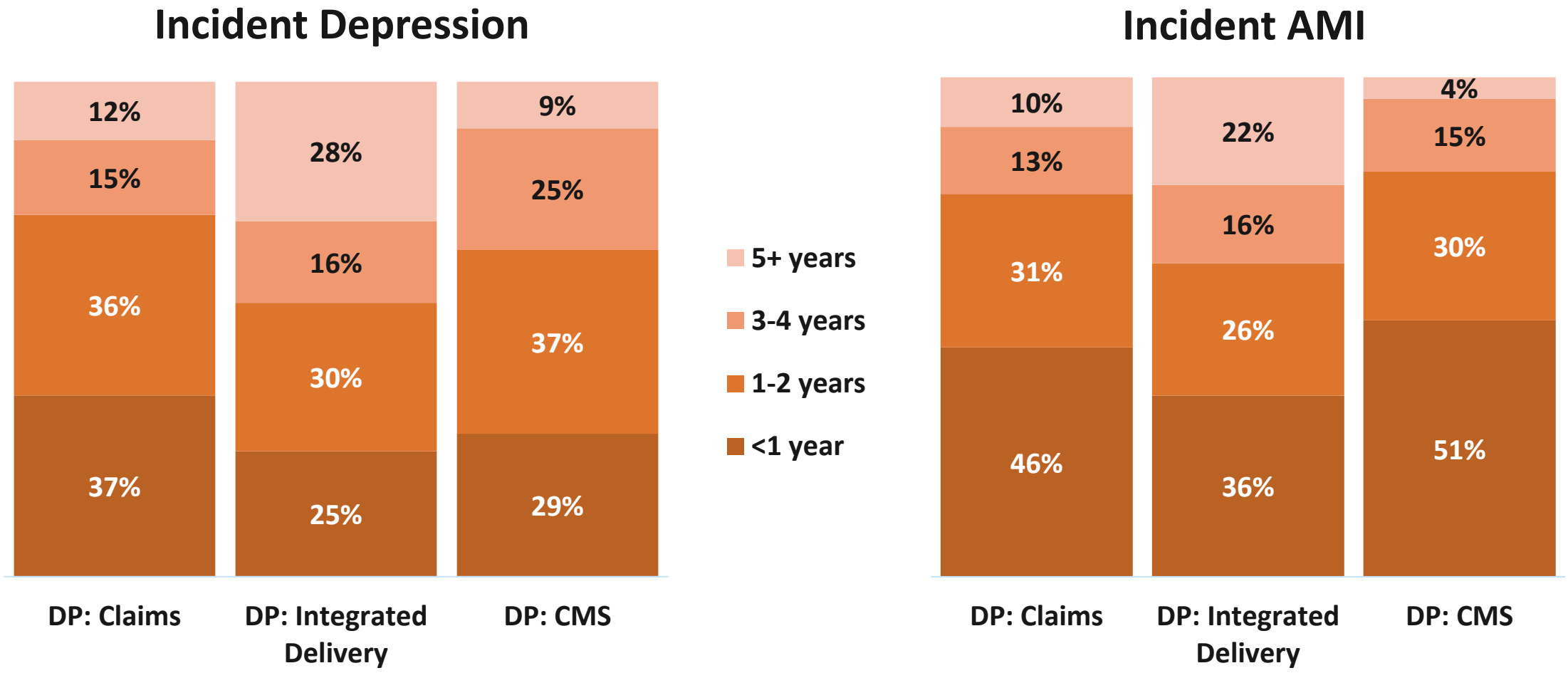
- Follow-up time is slightly longer for <19 and 65+ age group but depends on the chronic condition



*RA/OA: Rheumatoid Arthritis/Osteoarthritis

Follow-Up Time by Data Partner Type

- Integrated delivery systems have longer follow-up time than national commercial insurance and CMS DPs



Limitations

- Some modifications were made to adapt the CCW algorithm to the Sentinel Common Data Model

- CCW algorithms are widely used to characterize Medicare population
  - However, they have not been fully validated
  - Generalizability in non-Medicare populations may be limited

Summary

- Duration of follow-up varies by chronic condition, age, and DP type
  - Median follow-up ranges from <300 days to >800 days

- Application of CCW chronic condition algorithms can be used to estimate sample sizes and observation time for indicated disease cohorts in Sentinel prior to initiation of a query
  - They can also be used to describe baseline comorbid conditions in patients included in Sentinel drug safety studies

Questions?

info@sentinelsystem.org