



Experience from US FDA Sentinel Initiative Studies

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Disclosures

- I am funded by FDA to work in the Sentinel System

Collaborating Organizations

Lead – HPHC Institute

DEPARTMENT OF POPULATION MEDICINE



Data & Scientific Partners



Scientific Partners



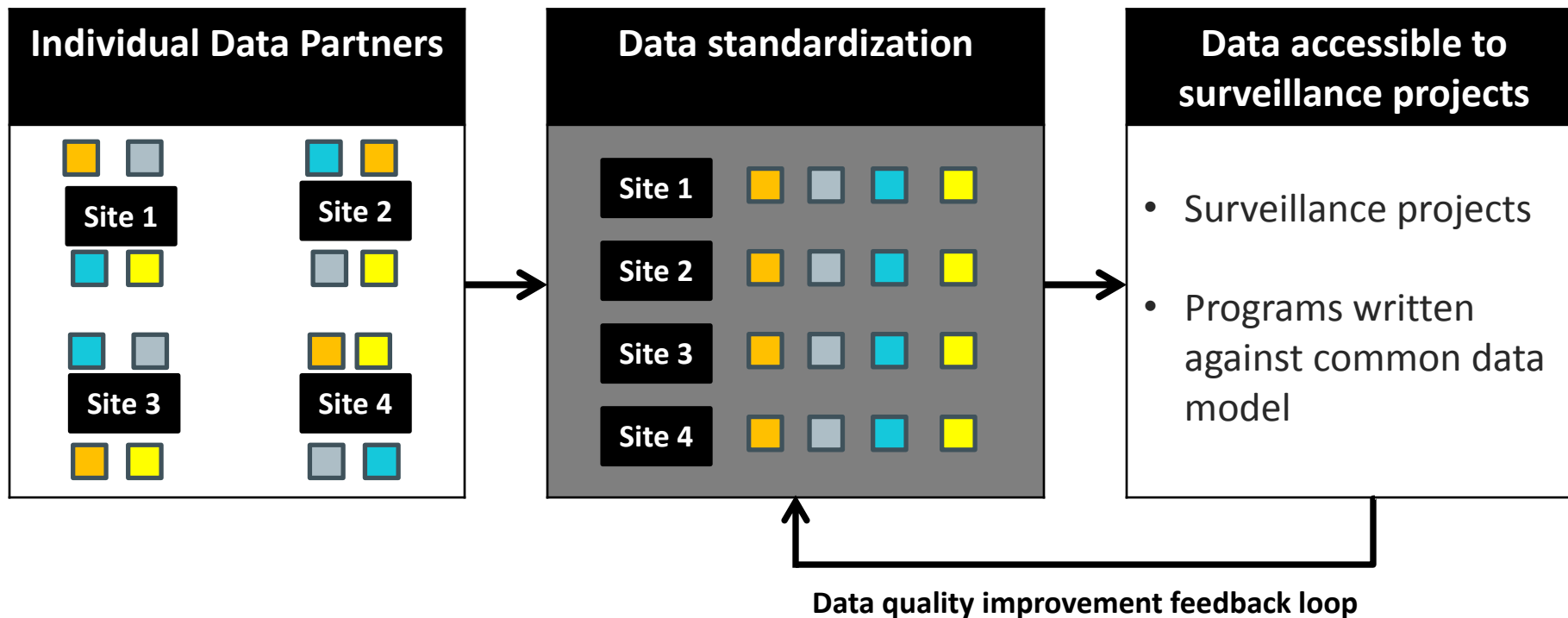
Sentinel approach to enhance validity & reduce heterogeneity

- Standardized data structure
- Robust data quality assurance process
- Pre-tested, customizable analytic tools
- Standardized analytic plan that also allows site-specific analysis

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Harmonizing multiple databases



Sentinel Common Data Model v7.0

Administrative Data						Clinical Data	
Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure	Lab Result	Vital Signs
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Enrollment Start & End Dates	Birth Date	Dispensing Date	Service Date(s)	Service Date(s)	Service Date(s)	Result & Specimen Collection Dates	Measurement Date & Time
Drug Coverage	Sex	National Drug Code (NDC)	Encounter ID	Encounter ID	Encounter ID	Test Type, Immediacy & Location	Height & Weight
Medical Coverage	Zip Code	Days Supply	Encounter Type and Provider	Encounter Type and Provider	Encounter Type and Provider	Logical Observation Identifiers Names and Codes (LOINC®)	Diastolic & Systolic BP
Medical Record Availability	Etc.	Amount Dispensed	Facility	Diagnosis Code & Type	Procedure Code & Type	Etc.	Tobacco Use & Type
			Etc.	Principal Discharge Diagnosis	Etc.		Etc.

Registry Data			Inpatient Data		Mother-Infant Linkage Data
Death	Cause of Death	State Vaccine	Inpatient Pharmacy	Inpatient Transfusion	Mother-Infant Linkage
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Mother ID
Death Date	Cause of Death	Vaccination Date	Administration Date & Time	Administration Start & End Date & Time	Mother Birth Date
Source	Source	Admission Date	Encounter ID	Encounter ID	Encounter ID & Type
Confidence	Confidence	Vaccine Code & Type	National Drug Code (NDC)	Transfusion Administration ID	Admission & Discharge Date
Etc.	Etc.	Provider	Route	Transfusion Product Code	Child ID
		Etc.	Dose	Blood Type	Child Birth Date
			Etc.	Etc.	Mother-Infant Match Method
					Etc.

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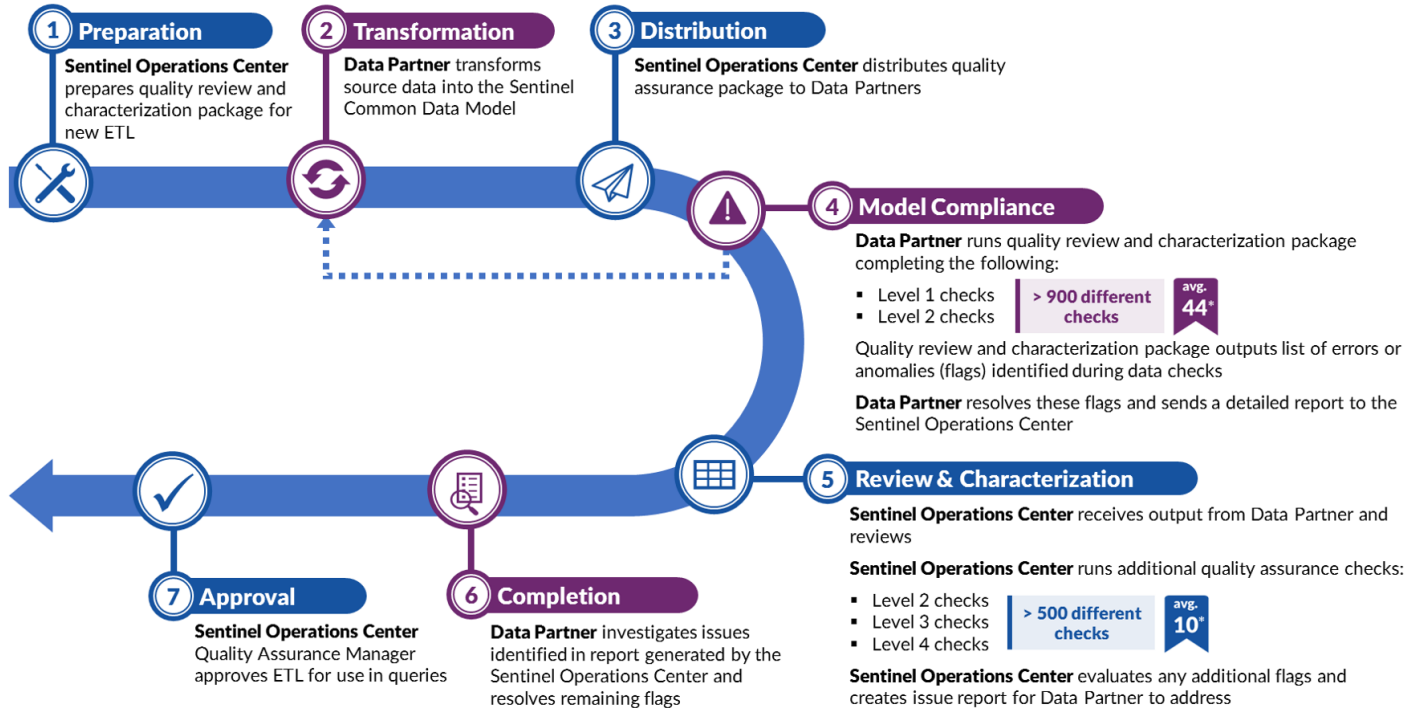
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FDA guidance on data quality assurance

Guidance for Industry and FDA Staff
Best Practices for Conducting
and Reporting
Pharmacoepidemiologic Safety
Studies Using Electronic
Healthcare Data

Sentinel data quality assurance practices

Sentinel Data Quality Review and Characterization Process



* On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL

- Consistent with FDA's best practices
- Data not used in any analysis unless passing QA
- **1,400+** checks per site per refresh

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Analytic framework (one-off)

Identify health plan members aged ≥ 18 years in year 2001-2014



Restrict to patients with a dispensing of oral ACEIs or β -blockers



Restrict to patients with ≥ 183 days health plan enrollment



Restrict to patients with no diagnosis of angioedema in prior 183 days



Follow patients from index date until diagnosis of angioedema or end of treatment

Analytic framework (re-usable)

Identify health plan members aged ≥ 18 years in year 2001-2014



Restrict to patients with a dispensing of oral ACEIs or β -blockers



Restrict to patients with ≥ 183 days health plan enrollment



Restrict to patients with no diagnosis of angioedema in prior 183 days



Follow patients from index date until diagnosis of angioedema or end of treatment

Analytic framework (re-usable)

Identify health plan members aged in year



Restrict to patients with a dispensing of or



Restrict to patients with days health plan enrollment

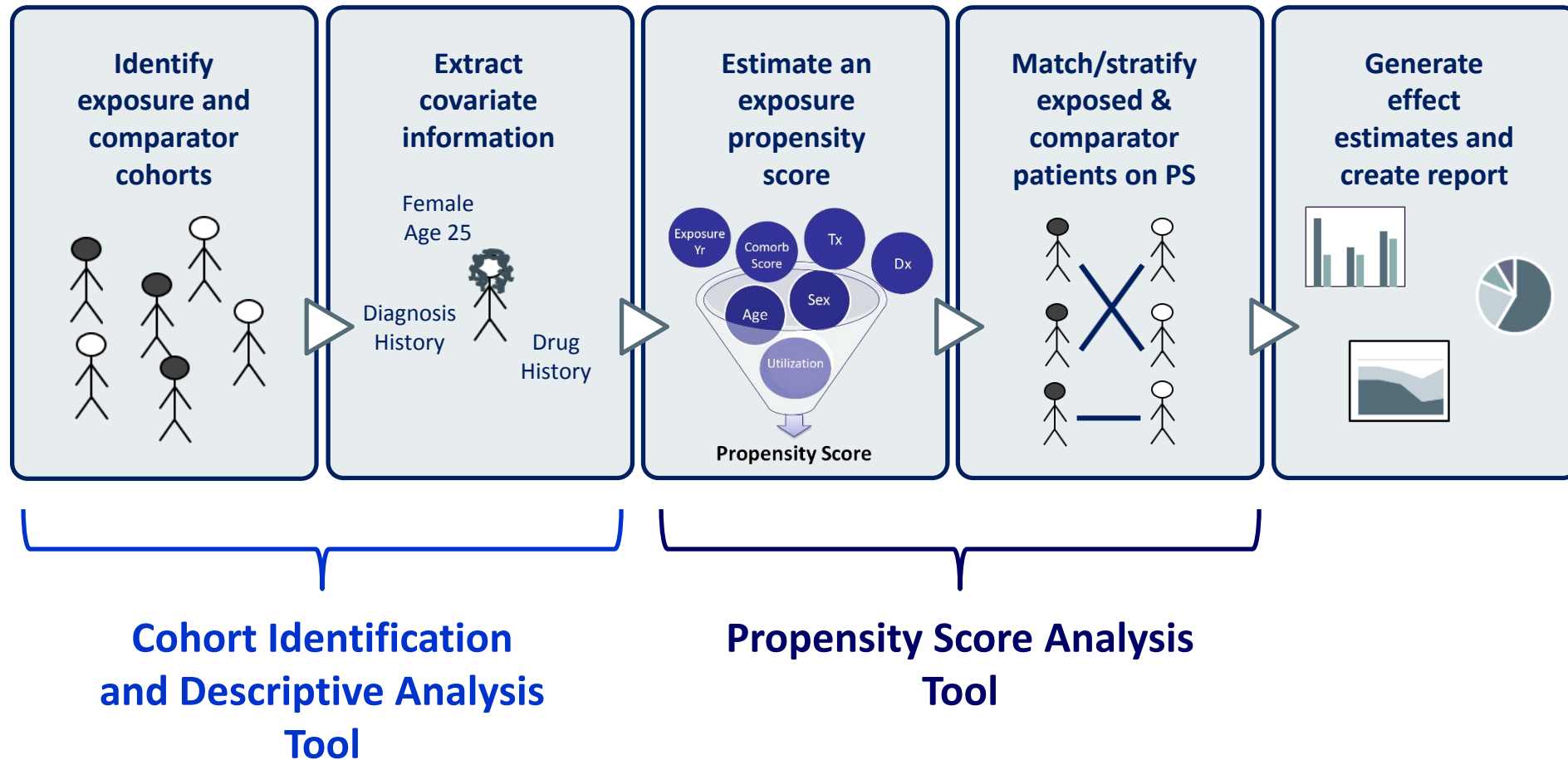


Restrict to patients with no diagnosis of in prior

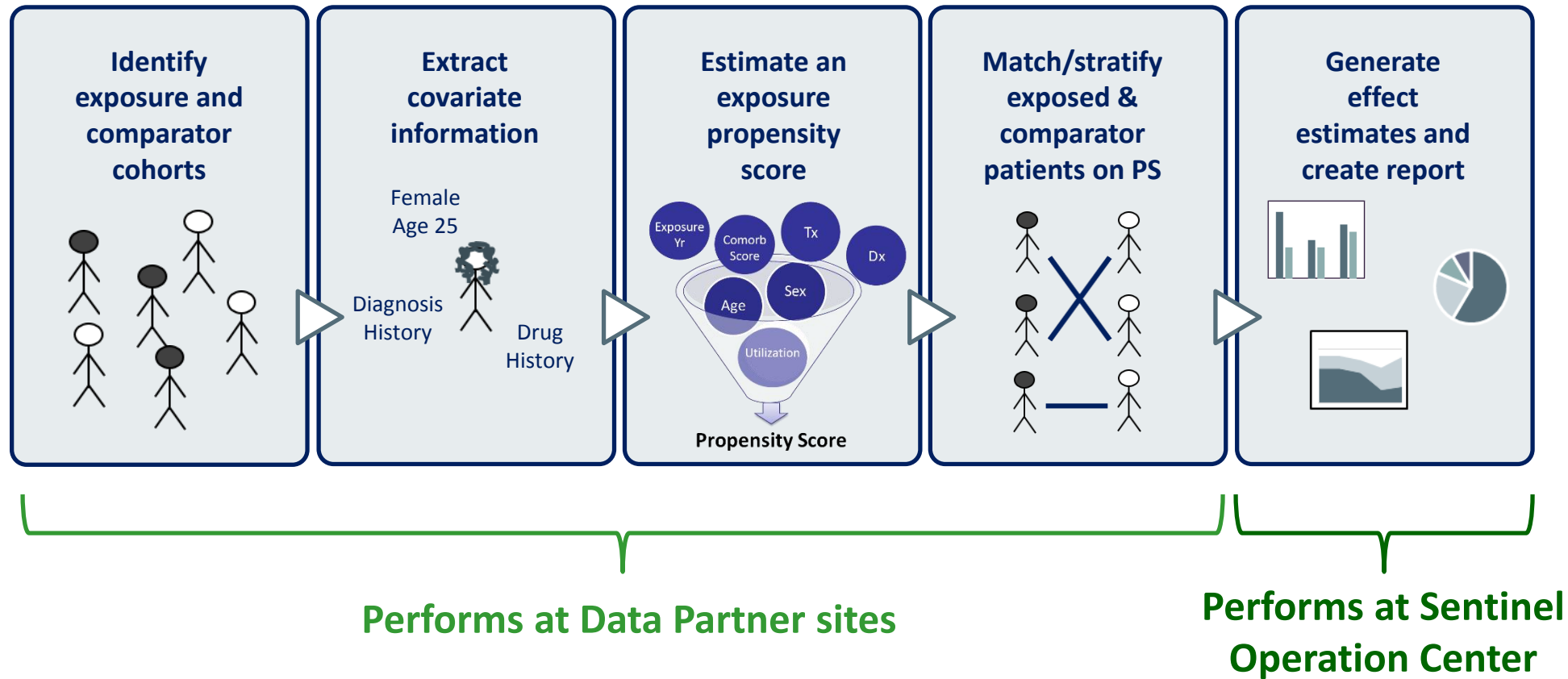


Follow patients from index date until diagnosis of or

Propensity score analysis in Sentinel



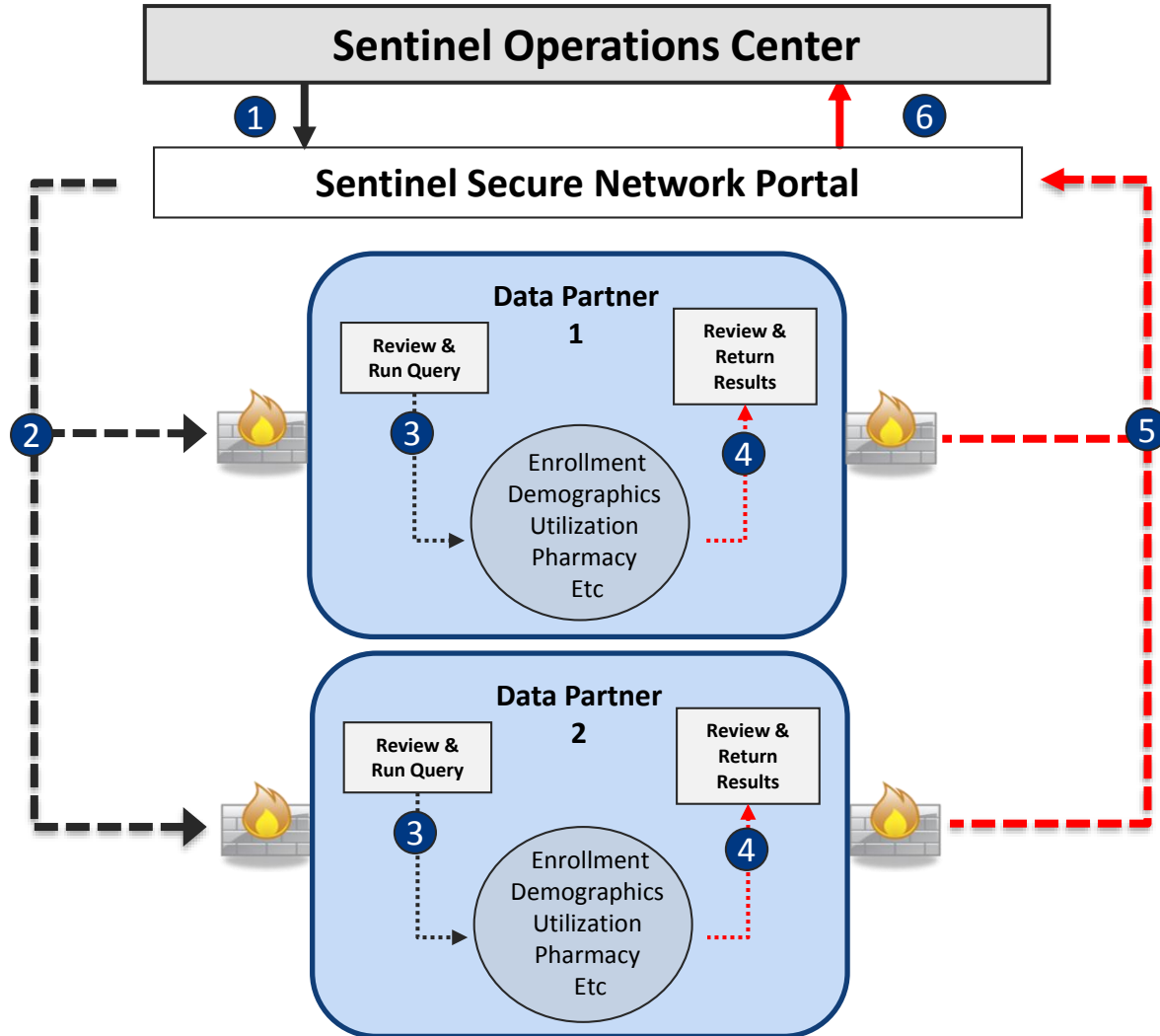
Propensity score analysis in Sentinel



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Distributed analysis in Sentinel



1. User creates and submits query
2. Data Partners retrieve query
3. Data Partners review and run query against their local data
4. Data Partners review results
5. Data Partners return results via secure network
6. Results are aggregated and reported

Additional analytic capabilities

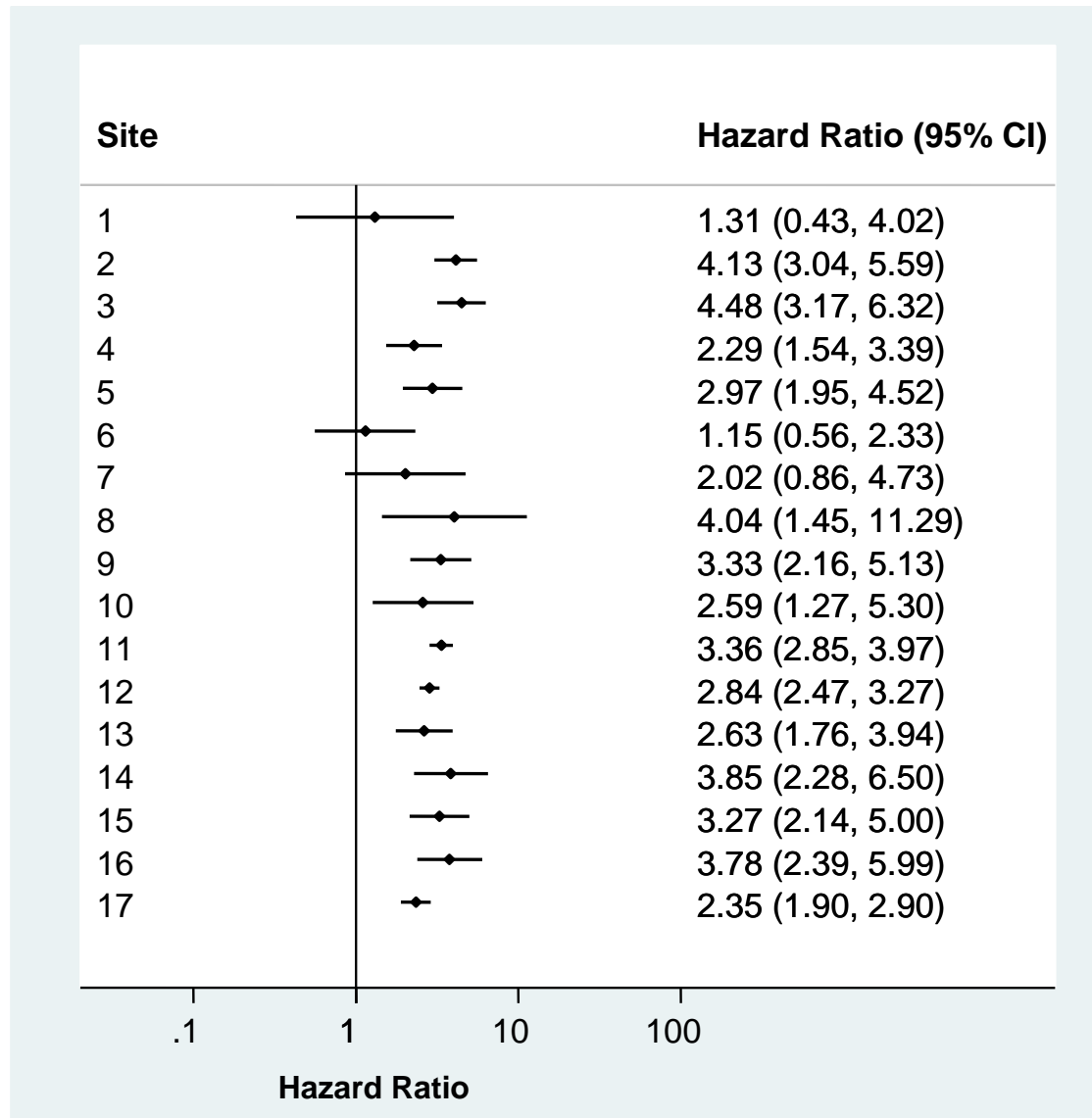
- Allow high-dimensional propensity scores
 - Database-specific covariate adjustment
- Allow pre-specify stratified or subgroup analysis
 - By Data Partner
 - By patient characteristic (e.g., age group, sex)
- Most analyses can be done with summary-level information
 - Risk-set based approaches (mathematically equivalent to pooled individual-level analysis)

Example 1 – Anti-hypertensive drugs and angioedema

Drug	Site-adjusted	PS-adjusted
ACEIs	2.77 (2.57, 2.98)	3.04 (2.81, 3.27)
ARBs	1.11 (0.97, 1.28)	1.16 (1.00, 1.34)
Aliskiren	2.75 (1.30, 5.81)	2.85 (1.34, 6.04)

Reference group: beta-blockers

Example 1 – Anti-hypertensive drugs and angioedema



ACEIs vs. beta-blockers

P-value for test for homogeneity: 0.01

Example 2 – Glyburide/glipizide vs. severe hypoglycemia

TABLE 3. Incidence Rates and Hazard Ratios of Emergency Department Visits and Hospital Admissions for Hypoglycemia

Exposure	New Users ^a	Person-Years at Risk	Serious Hypoglycemia Events	Incidence Rate per 1000 Person-Years	Hazard Ratio (95% CI)
Data from 13 data partners					
Unmatched ^b					
Glyburide	198,550	89,719	1,685	19	1.11 (1.05, 1.18)
Glipizide	379,507	244,094	5,406	22	—
Predefined covariates—unconditional model ^c					
Glyburide	173,655	83,108	1,633	20	1.35 (1.26, 1.45)
Glipizide	173,656	99,834	1,393	14	—
Predefined covariates—conditional model ^d					
Glyburide	173,655	38,986	1,064	27	1.36 (1.24, 1.49)
Glipizide	173,656	38,986	784	20	—

Example 2 – Glyburide/glipizide vs. severe hypoglycemia

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Exposure	New Users ^a	Person-Years at Risk	Serious Hypoglycemia Events	Incidence Rate per 1000 Person-Years	Hazard Ratio (95% CI)
Data from five data partners in which the hdPS model converged and completed without errors					
Unmatched ^b					
Glyburide	139,113	58,075	905	16	1.26 (1.16, 1.38)
Glipizide	181,911	94,941	1,079	11	—
Predefined covariates—unconditional model ^c					
Glyburide	120,334	53,366	859	16	1.41 (1.27, 1.56)
Glipizide	120,335	61,552	666	11	—
Predefined covariates—conditional model ^d					
Glyburide	120,334	24,708	568	23	1.42 (1.25, 1.62)
Glipizide	120,335	24,708	399	16	—
hdPS—unconditional model ^c					
Glyburide	116,930	52,816	870	17	1.50 (1.36, 1.66)
Glipizide	116,931	62,526	644	10	—
hdPS—conditional model ^d					
Glyburide	116,930	24,494	581	24	1.49 (1.31, 1.70)
Glipizide	116,931	24,498	389	16	—

Example 2 – Glyburide/glipizide vs. severe hypoglycemia

eTable 2. Hazard ratios of emergency department visits and hospital admissions for hypoglycemia by site.

Hazard Ratio (95%CI) ^{a, b}	Unmatched	Predefined covariates –		hdPS –		Predefined covariates and	
		Unconditional model ^c	Predefined covariates – Conditional model ^d	Unconditional model ^c	hdPS – Conditional model ^d	hdPS – Unconditional model ^c	Predefined covariates and hdPS – Conditional model ^d
Data partner 1	1.31 (1.13-1.52)	1.47 (1.24, 1.75)	1.47 (1.18, 1.83)	1.58 (1.33, 1.88)	1.60 (1.29, 2.00)	1.50 (1.26, 1.78)	1.42 (1.14, 1.76)
Data partner 2	1.48 (1.26, 1.74)	1.76 (1.46, 2.12)	1.71 (1.35, 2.18)	1.71 (1.43, 2.06)	1.61 (1.27, 2.04)	1.79 (1.48, 2.16)	1.77 (1.39, 2.26)
Data partner 3	1.18 (0.72, 1.96)	1.59 (0.84, 3.01)	1.67 (0.73, 3.81)	---	---	---	---
Data partner 4	1.57 (0.86, 2.86)	1.53 (0.75, 3.12)	2.60 (0.93, 7.29)	1.87 (0.85, 4.08)	1.80 (0.60, 5.37)	2.00 (0.92, 4.34)	2.40 (0.85, 6.81)
Data partner 5	1.61 (0.80, 3.23)	1.33 (0.54, 3.27)	1.75 (0.51, 5.98)	---	---	---	---
Data partner 6	17.72 (2.04, 153.9)	6.60 (0.75, 58.07)	72*13 (0.00, .)	---	---	---	---
Data partner 7	1.09 (0.54, 2.20)	1.41 (0.59, 2.88)	0.71 (0.23, 2.25)	1.19 (0.43, 3.27)	1.25 (0.34, 4.65)	1.19 (0.43, 3.27)	1.50 (0.42, 5.32)
Data partner 8	1.32 (1.19, 1.47)	1.38 (1.23, 1.56)	1.41 (1.21, 1.64)	---	---	---	---
Data partner 9	0.44 (0.66, 3.23)	1.03 (0.06, 16.51)	. (., .)	---	---	---	---
Data partner 10	3.33 (1.27, 8.72)	2.30 (0.53, 9.91)	4.00 (0.45, 35.79)	---	---	---	---
Data partner 11	0.55 (0.47, 0.65)	0.96 (0.77, 1.19)	0.85 (0.63, 1.13)	---	---	---	---
Data partner 12	3.52 (1.28, 9.68)	2.90 (0.51, 16.34)	1.00 (0.14, 7.10)	---	---	---	---
Data partner 13	1.03 (0.88, 1.21)	1.10 (0.92, 1.31)	1.16 (0.93, 1.45)	1.24 (1.04, 1.49)	1.29 (1.04, 1.61)	1.24 (1.04, 1.49)	1.29 (1.04, 1.61)

hdPS – High-dimensional propensity score, CI – Confidence interval.

^a Hazard ratios comparing glyburide versus. glipizide.

^b Please note, one data partner removed a small number of users that moved to administrative services only plans. Information from these users is included in Tables 1 and 2, but removed from subsequent tables.

^c The conditional models were stratified by the matched pair.

^d The unconditional models were not stratified by the matched pair.

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- Minimize variations in data quality, design, and analysis
- Any observed differences in results across sites would more likely indicate real treatment effect heterogeneity

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<https://www.distributedanalysis.org>