Modular Programs

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Mini-Sentinel Methods Core
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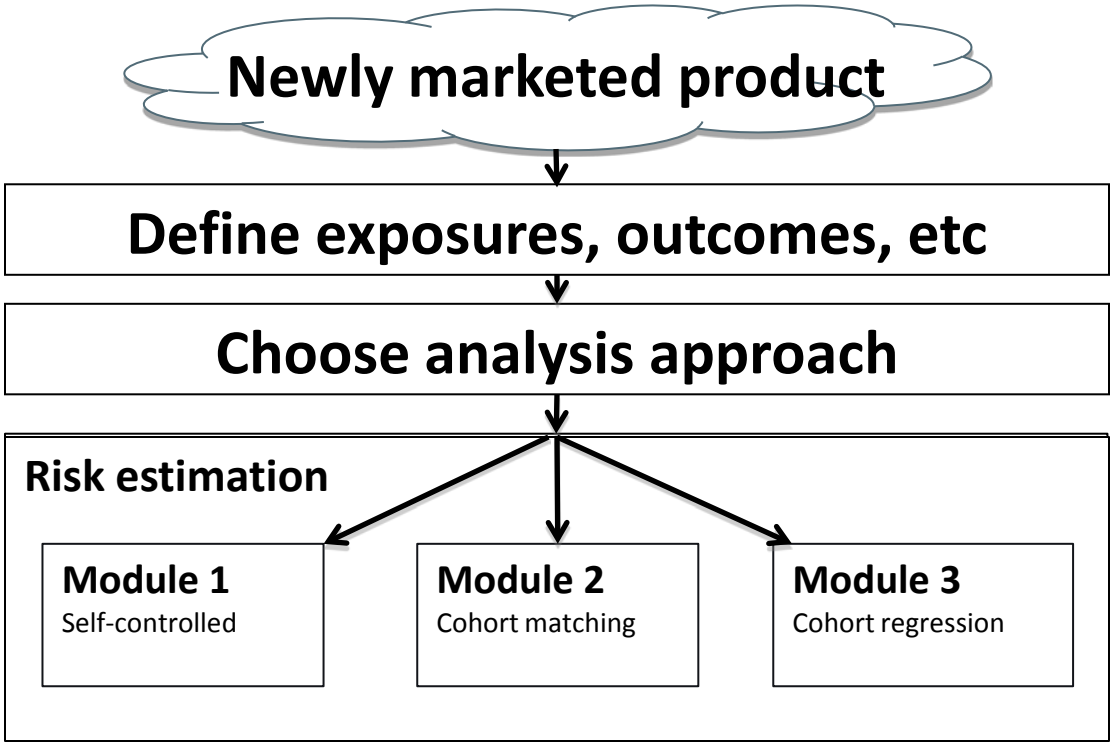
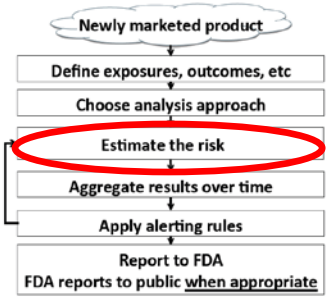
Modular approach to drug safety monitoring in a distributed database system

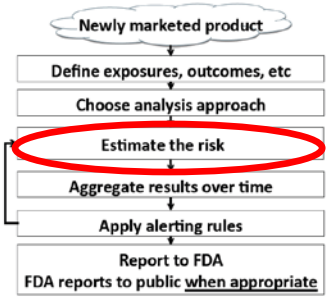
- Principal idea
  - Pre-programmed modules can be quickly activated to run adjusted analyses across data partners
  - For monitoring, modules will be run repeatedly as data are refreshed
- Some specifications
  - Validated programming code
  - Can be run asynchronously across data partners as data get refreshed while preserving data privacy
  - Confounding adjustments via self-controlled designs, PS matching or regression analyses
  - Estimate ratio and difference measures (rate or risk)
  - Sequential (or group sequential) analyses

Prospective surveillance: estimate risk





Prospective surveillance: estimating risk



Module 1

Index identification

Self-controlled

Key parameters:

-Exposure crossover

-Risk and control window

-Exposure time trend adjustment

Module 2 **Module 3**

Cohort identification (MP3)

Cohort Matching

Key parameters:

-Score-based matching (PS, DRS)

-hd-PS

-1:1/variable ratio

-AT vs. ITT

Cohort Regression

Key parameters:

-Regression

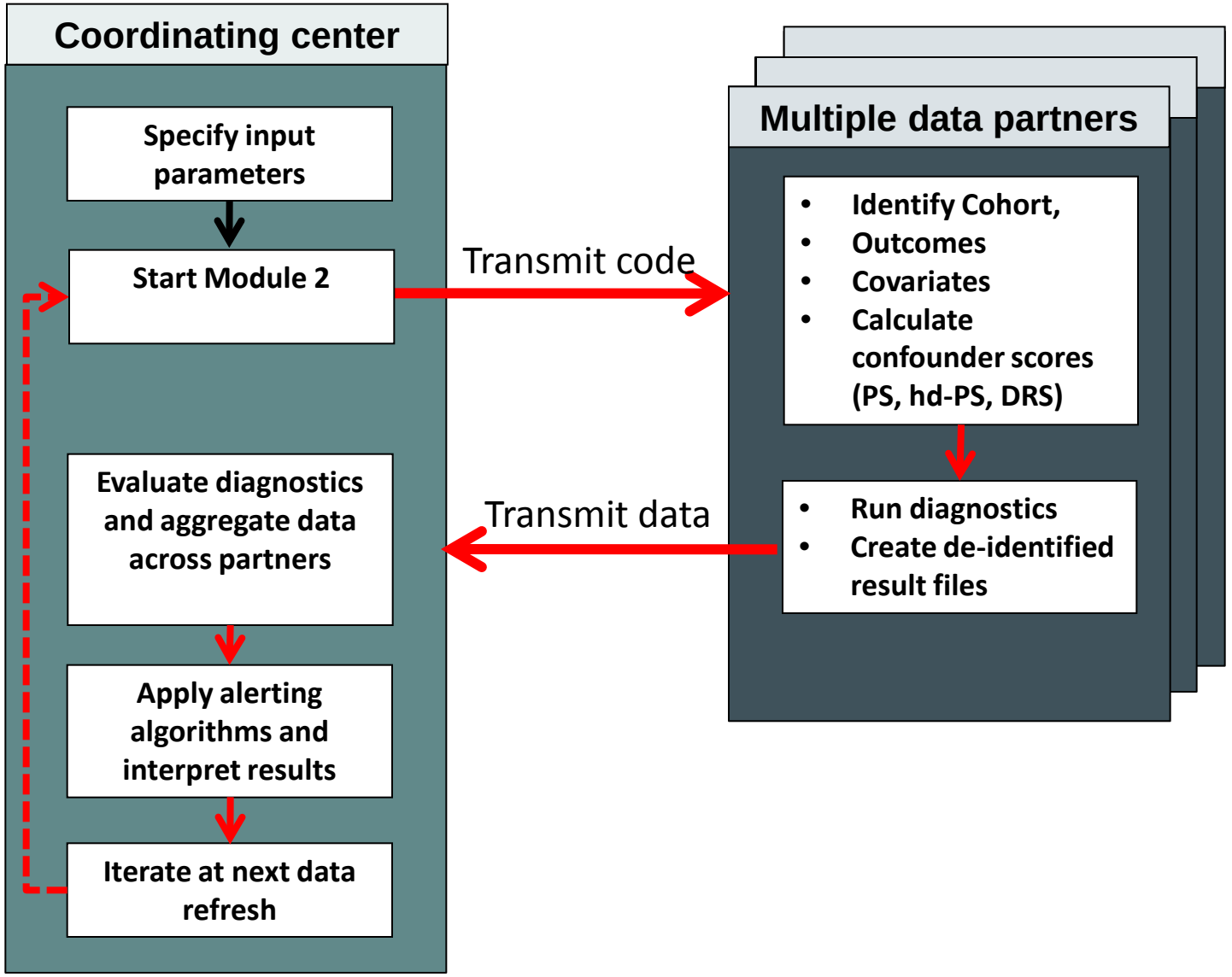
-IPT weighted regression

-Tailored to the rare event setting

Sensitivity analyses

- Popn. Subgroups
- Dose subgroups

Module 2 in detail

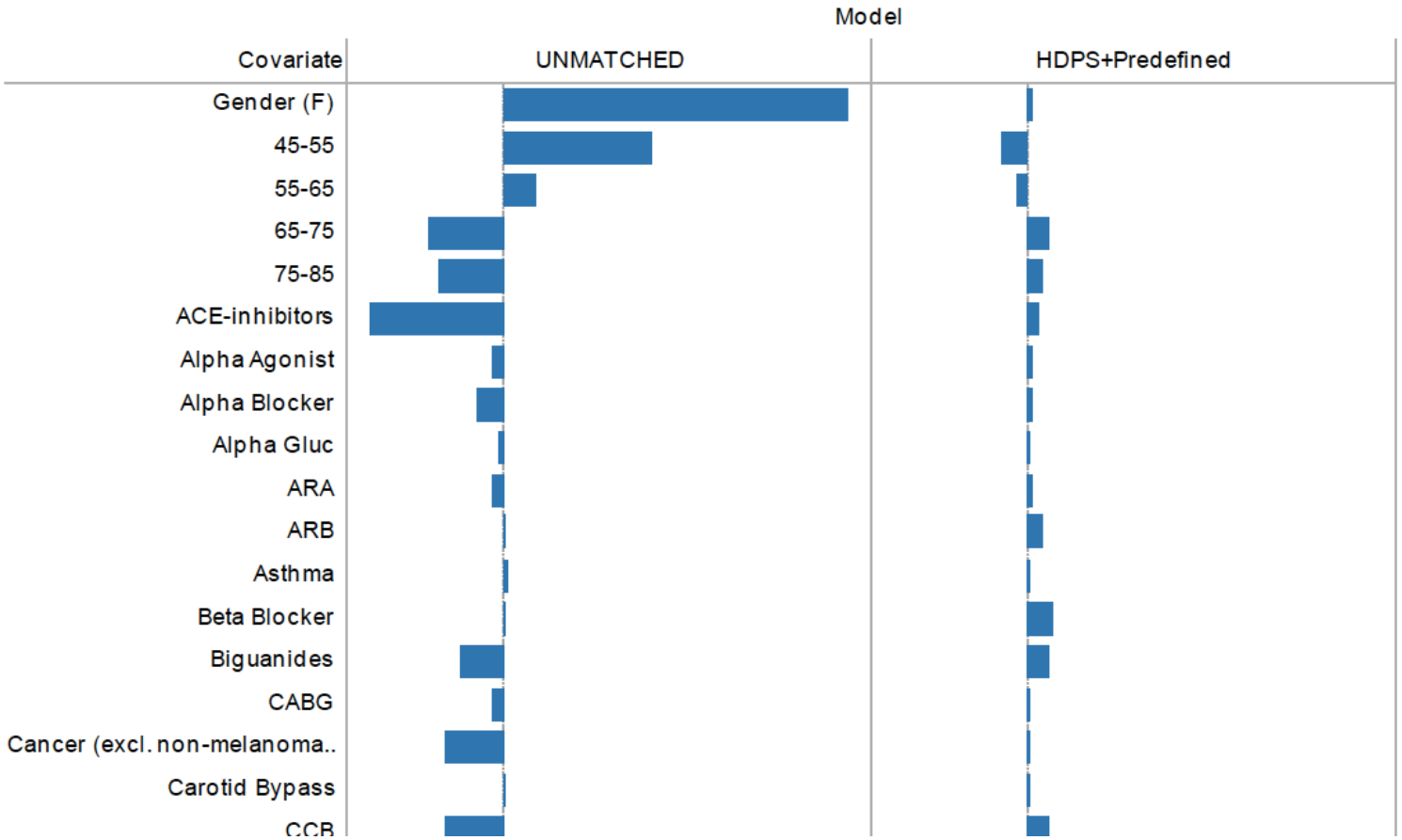


Diagnostics: Balance before matching

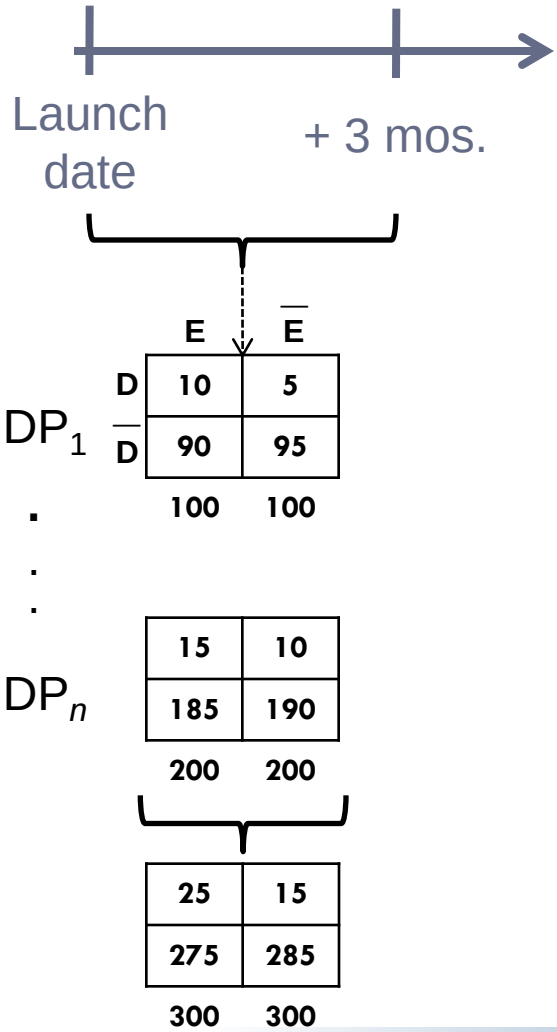
Table 1. Cohort of New Initiators of Rofecoxib and Non-Selective NSAID (Unmatched)

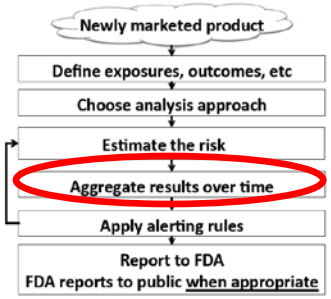
	Primary Analysis		Covariate Balance	
			Absolute	Standardized
	N (%)	N (%)	Difference	Difference
Characteristic	rofecoxib	nsaid		
Number of patients	9409 (100.0 %)	9977 (100.0 %)		
Number of Events While on Therapy	39 (0.4 %)	15 (0.2 %)		
Person time at risk	59.9 (33.3)	46.4 (32.5)		
Patient Characteristics				
Age	76.3 (10.7)	73.1 (12.2)	3.2	3.2
60-70	1305 (13.9 %)	1679 (16.8 %)	-2.9	-0.082
70-80	3631 (38.6 %)	3883 (38.9 %)	-0.3	-0.007
80-90	3179 (33.8 %)	2619 (26.3 %)	7.5	0.164
90-100	580 (6.2 %)	395 (4.0 %)	2.2	0.101
Gender (F)	7764 (82.5 %)	7374 (73.9 %)	8.6	0.208
Recorded use of:				
Ace Inhibitors	1224 (13.0 %)	1351 (13.5 %)	-0.5	-0.016
ARB	567 (6.0 %)	535 (5.4 %)	0.6	0.029
Anticoagulants	548 (5.8 %)	328 (3.3 %)	2.5	0.122
And many more …	⋮	⋮	⋮	

Diagnostics: Balance before/after matching

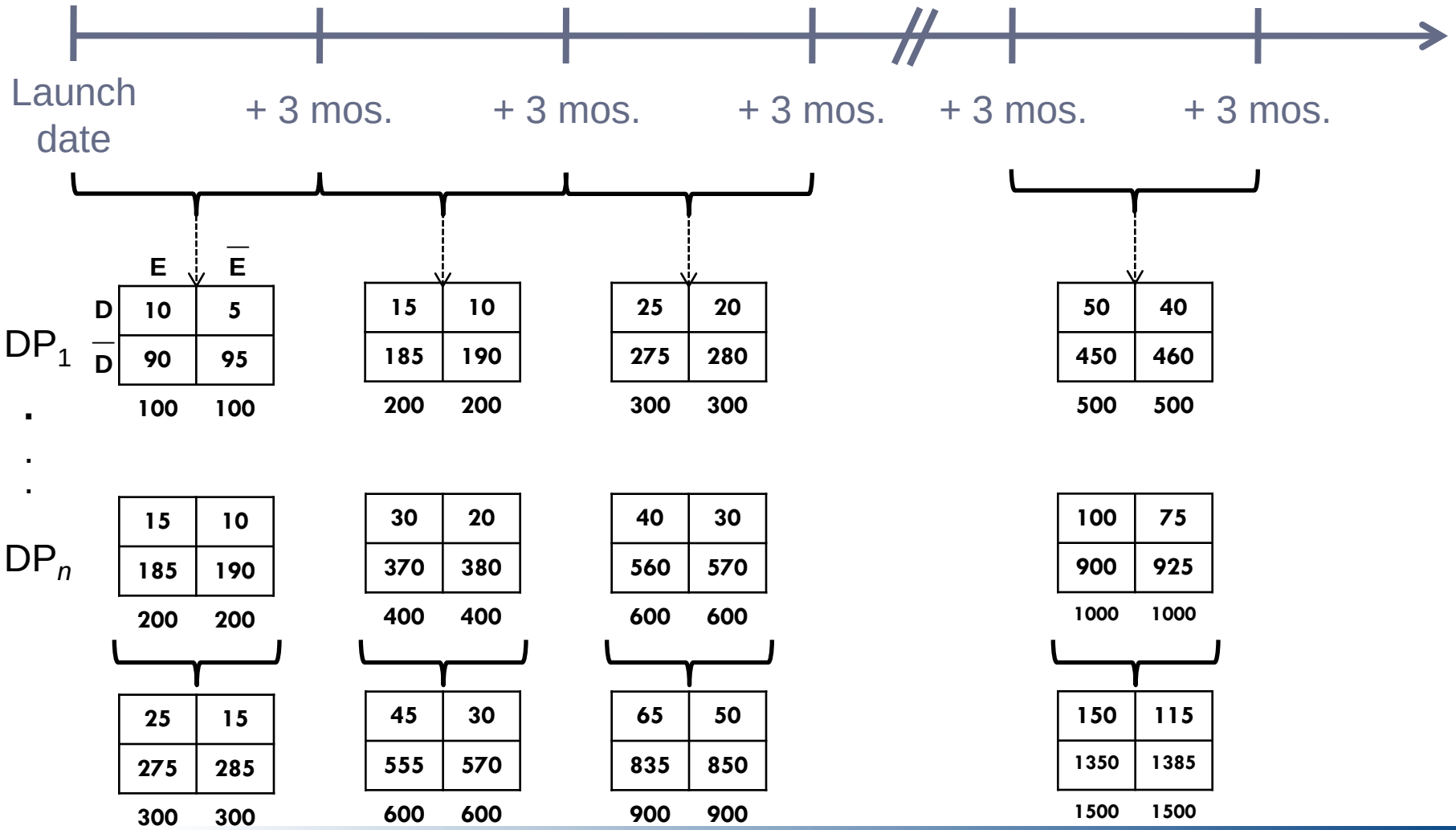


Data **aggregation** across data partner

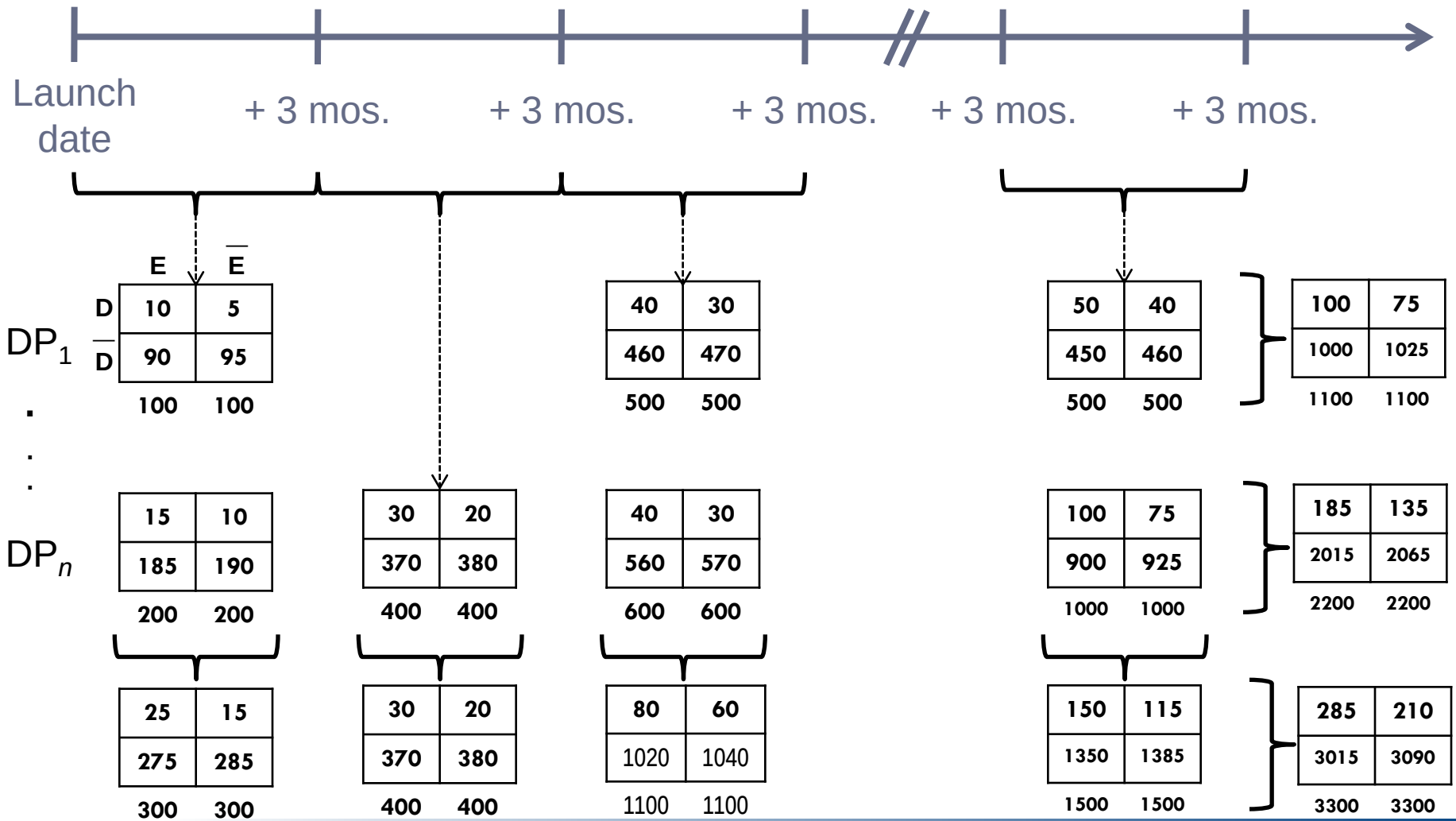




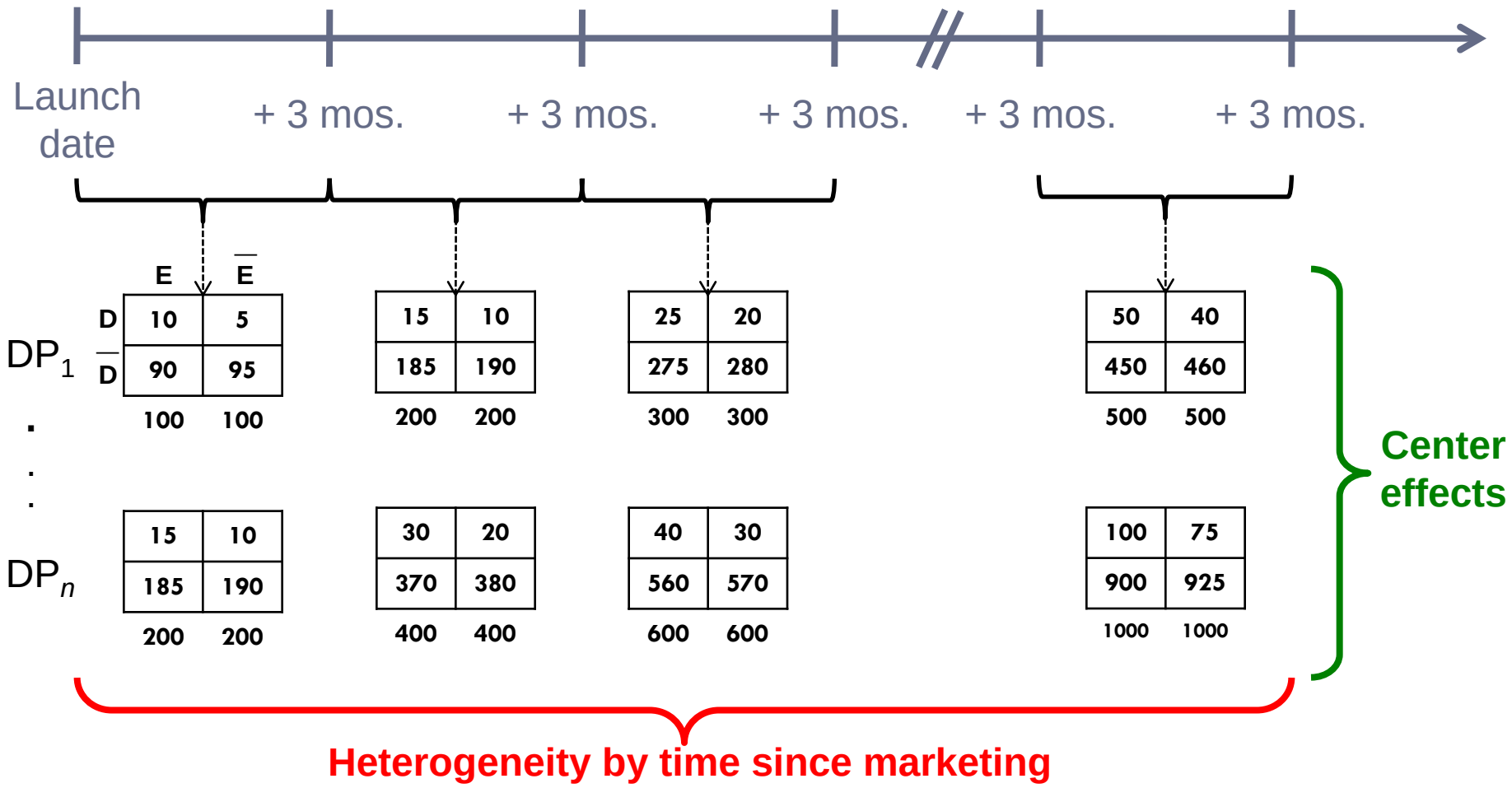
Data aggregation across DPs & over time



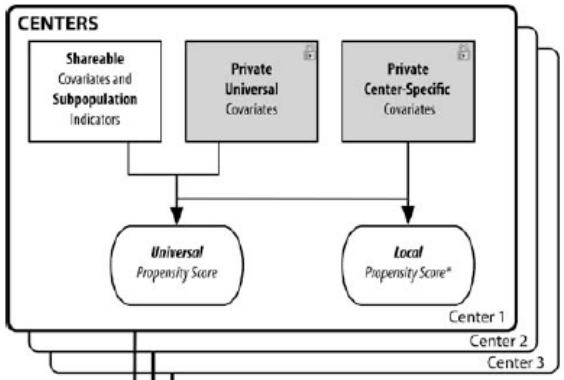
Asynchronous database refreshes



Visualizing heterogeneity



Data aggregation (Report: Rassen et al.)



CENTER TO HUB TRANSFER FILE

ctr id	pat id	exp	out-come	age_ decade	white	sex	ps_ univ	ps_ local
3	1	0	0	70	Y	F	0.32	0.29
3	2	1	0	60	N	F	0.68	0.72
3	3	1	1	50	N	F	0.74	0.61
3	4	0	0	60	Y	M	0.23	0.38

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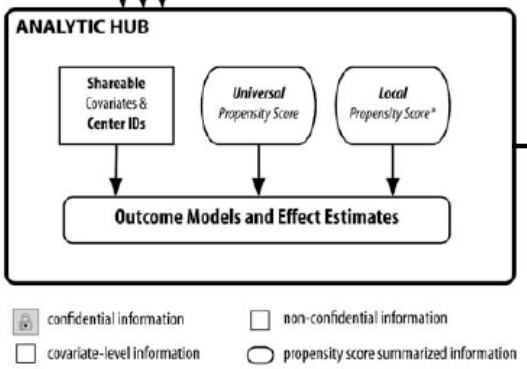
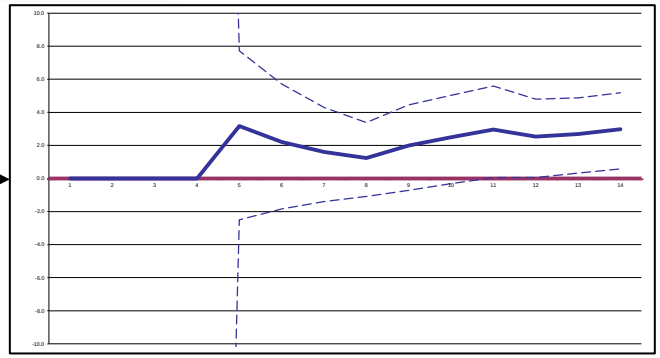
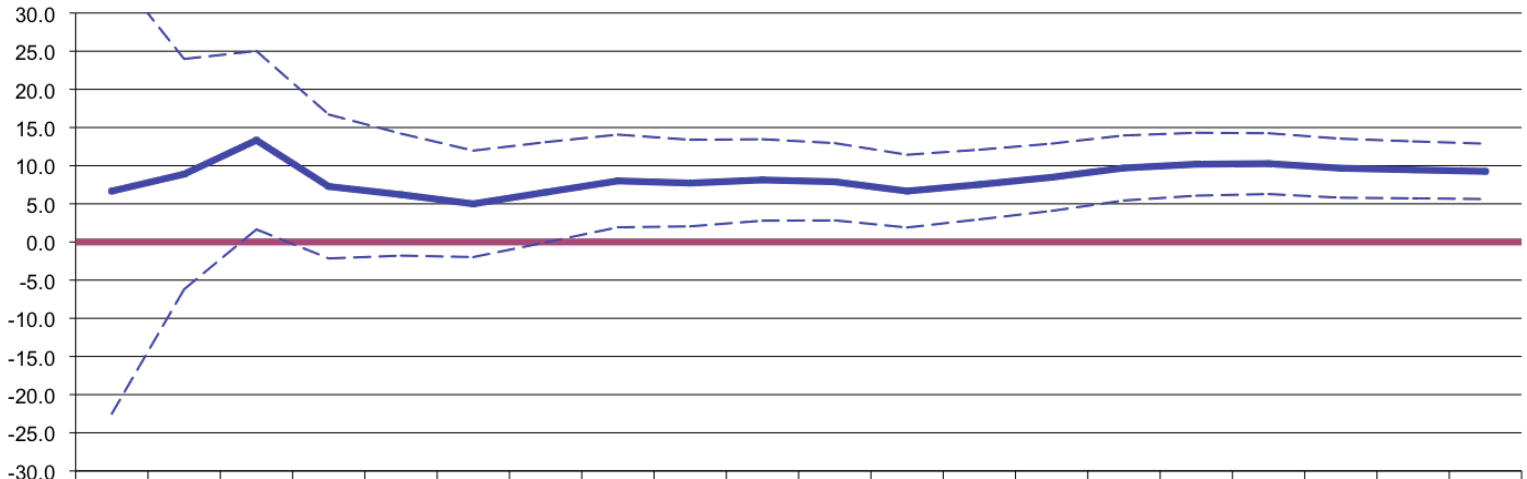


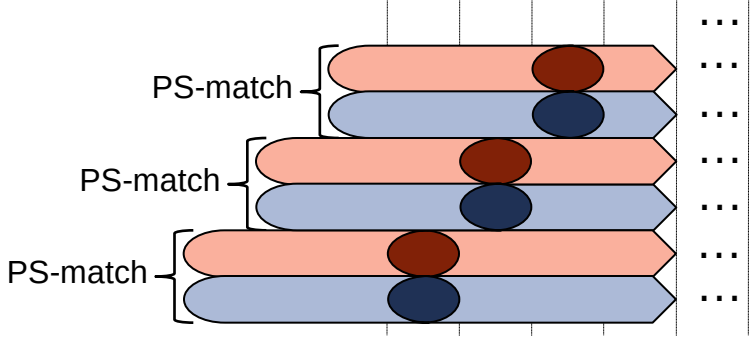


Rassen JA, et al. *Pharmacoepidemiol Drug Saf* 2010;19:848-57

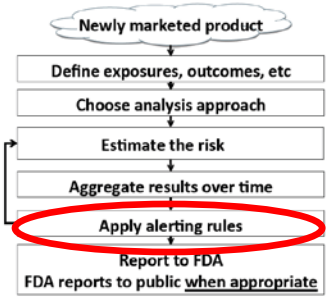
Aggregation over time



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16	-1.79	-1.97	-0.06	1.93	2.05	2.79	2.83	1.90	2.96	4.07	5.43	6.07	6.28	5.80	5.72	5.62
Cumulative rate difference	6.67	8.89	13.33	7.27	6.21	5.00	6.51	8.00	7.72	8.13	7.89	6.67	7.53	8.48	9.70	10.19	10.27	9.67	9.45	9.25
Upper 95% confidence interval	35.88	23.98	25.02	16.70	14.20	11.97	13.08	14.07	13.39	13.46	12.95	11.43	12.09	12.89	13.96	14.31	14.25	13.53	13.18	12.88
Cumulative events: monitoring drug	3	8	15	18	22	25	33	40	45	51	56	58	65	73	82	89	95	99	103	108
Cumulative events: comparator drug	2	4	5	10	13	16	19	20	23	25	28	32	33	34	34	35	37	41	43	46
Cumulative person-years: monitoring drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700
Cumulative person-years: comparator drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700



Prospective surveillance: alerting



Risk estimation

Module 1
Self-controlled

Module 2
Cohort matching

Module 3
Cohort regression

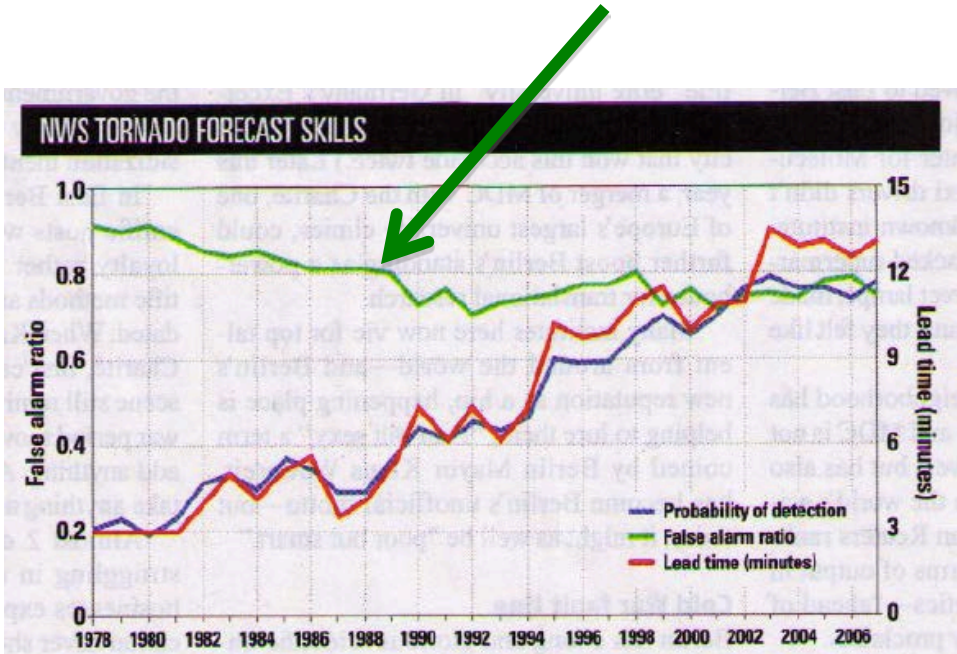
Sensitivity analyses

Aggregate accumulating results over time

Apply **alerting rules**

Pre-monitoring activities

- Acceptable false positive rate may vary:
- Acceptable level of risk
  - Availability of alt. meds
  - Severity of event(s)
  - Expected beneficial effect
- Anticipated utilization
  - Monitoring intervals
  - Duration of monitoring

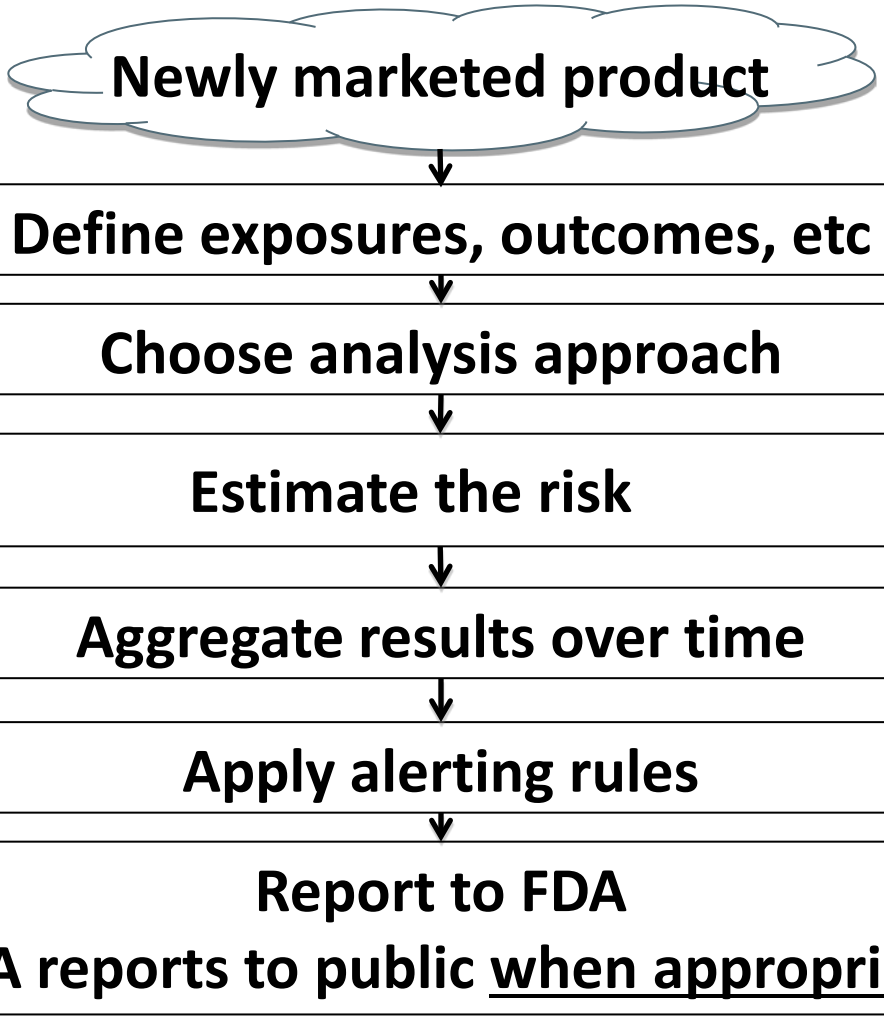


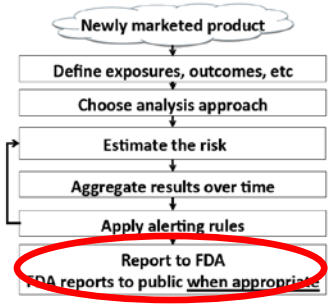
Progress, or not. The U.S. National Weather Service has increased its tornado warning time (lead time, red), thanks to Doppler radar. But the false alarm ratio—how often forecasters warned of a tornado that never appeared—hasn't budged in 20 years.

Post-monitoring activities

- Sensitivity analyses
  - Confounding
  - Exposure risk-window
  - Incident user definition window
  - AT vs. ITT
- Subgroup analyses as needed
- Comprehensive presentation of decision-relevant information

Prospective surveillance: reporting

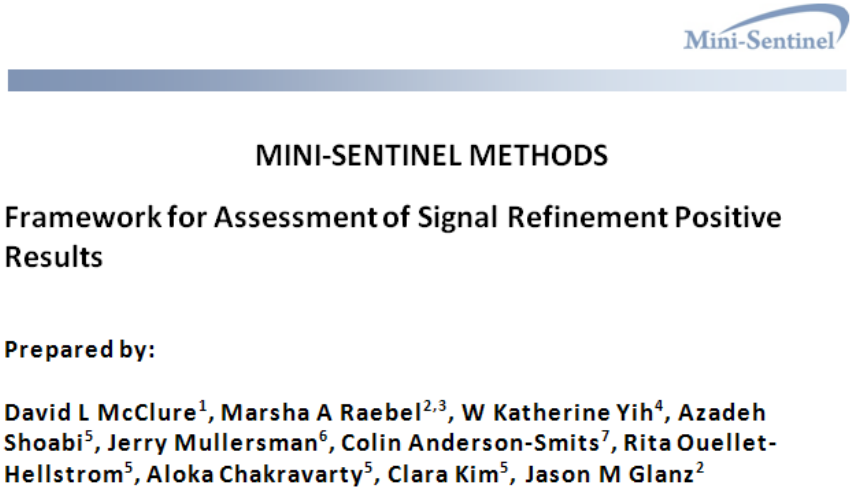




What happens when we find something?

- Prompt, pre-planned product-specific assessment of positive signal

- Examples of follow-up activities:
  - Data validity checks, analytic code checks
  - Adjust for additional confounders
  - Test against other comparators
  - Medical chart validation of cases
  - Quantitative bias analysis
  - Detailed epidemiologic investigation to assess causality


Mini-Sentinel

MINI-SENTINEL METHODS

Framework for Assessment of Signal Refinement Positive Results

Prepared by:

David L McClure[1], Marsha A Raebel[2,3], W Katherine Yih[4], Azadeh Shoabi[5], Jerry Mullersman[6], Colin Anderson-Smits[7], Rita Ouellet-Hellstrom[5], Aloka Chakravarty[5], Clara Kim[5], Jason M Glanz[2]