ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Roundtable on Active Medical Product Surveillance

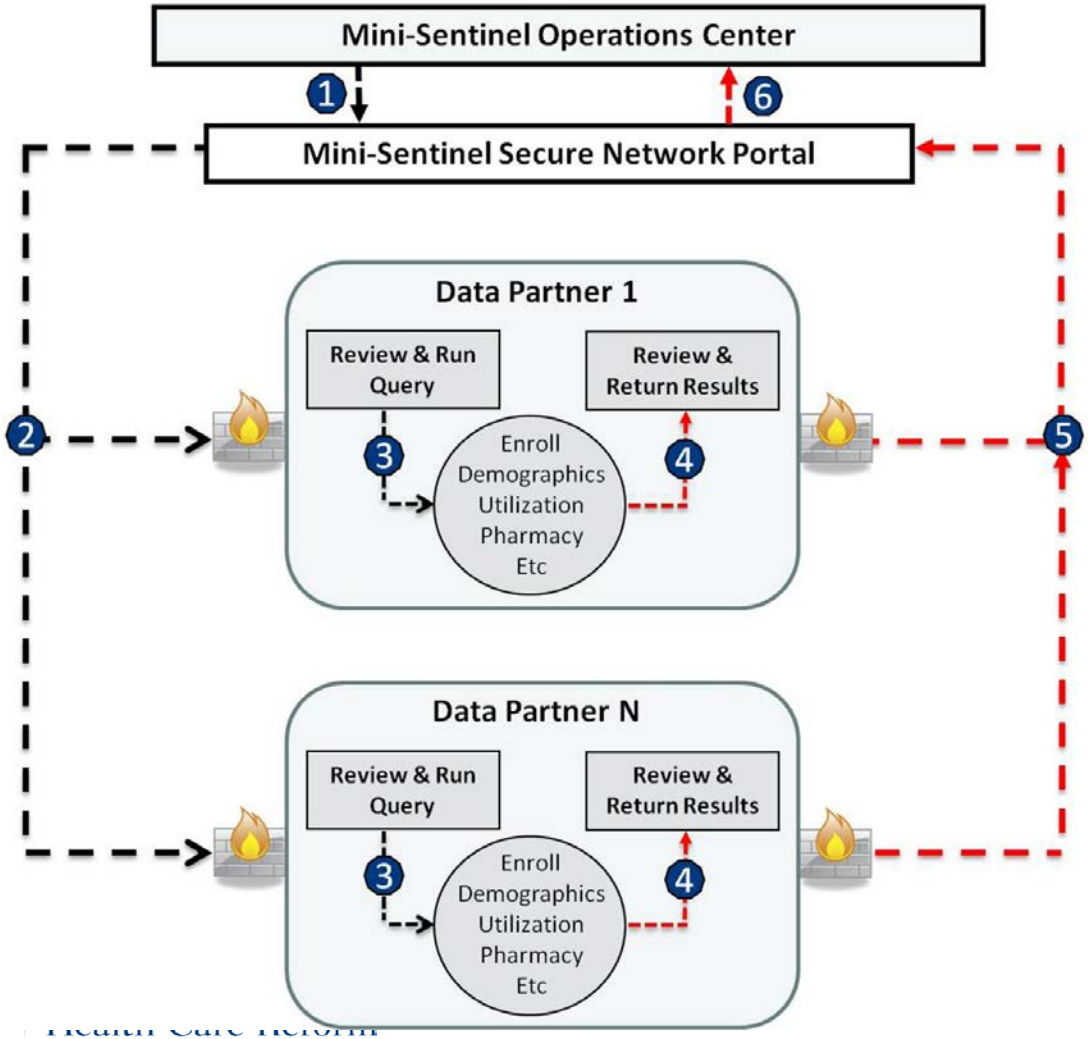
An Overview of the Design and Implementation of FDA's Prospective Routine Observational Monitoring Program Tools for Safety Surveillance

Jennifer Nelson, Group Health Research Institute and University of Washington

Elizabeth Chrischilles, University of Iowa Department of Epidemiology

Monday, September 16, 2013

Mini-Sentinel's Distributed Database



1- User creates and submits query (a computer program)

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

Source: Mini-Sentinel

Mini-Sentinel Analyses

Modular Programs

- Rapid assessments
- Near real-time
- Executed by each data partner behind their firewall
- For additional information, please see the Mini-Sentinel Presentation on Modular Programs

Protocol-Based Assessments

- Formal and detailed evaluations
- Customized study designs and protocols
- More resource- and time- intensive than modular programs
- For examples of past Mini-Sentinel Protocol-Based Assessments, please see here or here

Prospective Routine Observational Monitoring Program Tools (PROMPT)

- Relatively standardized
- Semi-automated
- Routine prospective surveillance program
- Can examine a number of products simultaneously

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PROMPT: Prospective Routine Observational Monitoring Program Tools

Elizabeth Chrischilles, U of Iowa
Jennifer Nelson, Group Health and U of WA
Mini-Sentinel Protocol Core and Methods Core

September 16, 2013

FDA's Vision for a Semi-Automated Surveillance System as Another Surveillance Tool

What constitutes a comprehensive safety surveillance system?

- Semi-automated routine surveillance, applying general tools with minor adaptations to address the specific product

But also…

- Ability to bring specialized expertise to bear on specific issue(s) that may arise in product lifecycle

Complements other approaches

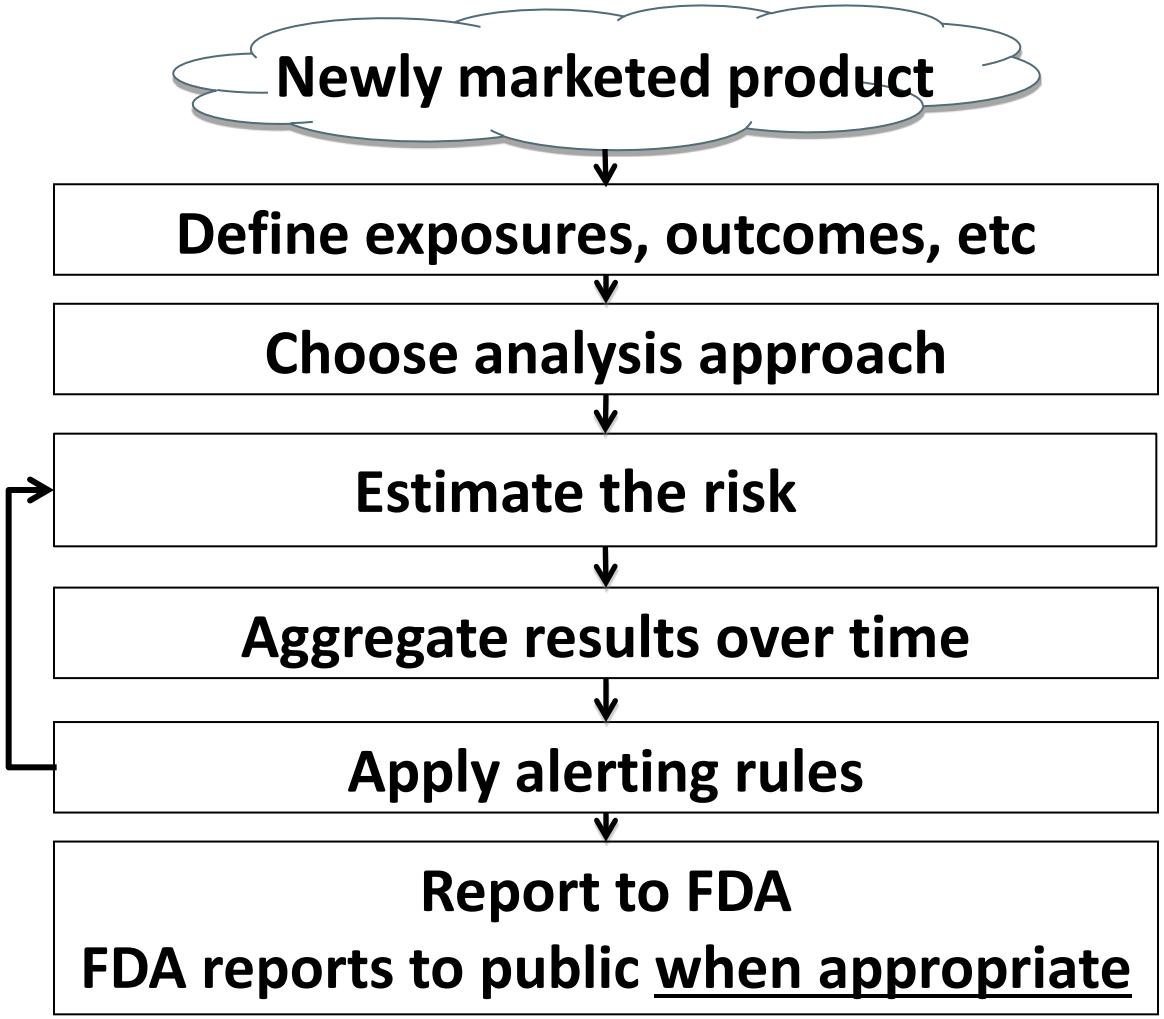
- Other Mini Sentinel activities
  - describe populations and treatment (e.g., uptake)
  - one-time, retrospective customized protocol-based assessments for older products
  - monitor impact of FDA actions (e.g., a label change)
- FDA activities beyond Mini Sentinel
  - surveillance based on spontaneous reports
  - untargeted surveillance (data mining) of healthcare data
  - customized protocol-based studies using healthcare data

Overview of Anticipated Procedures for Active Surveillance of New Medical Products Using the PROMPT System

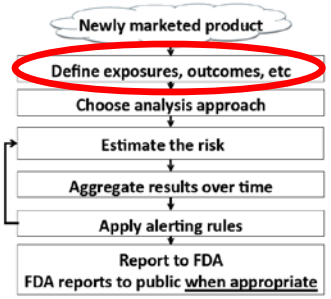
Goal

- Relatively standardized
- Prospective
- A number of products simultaneously
- Signal *potential* excess risk for subsequent follow-up
- Tools:
  - Cohort and outcome library
  - Core confounder definition
  - Module selection tool
  - Analysis modules
  - User guides

PROMPT surveillance at a glance



PROMPT surveillance: who, what, when



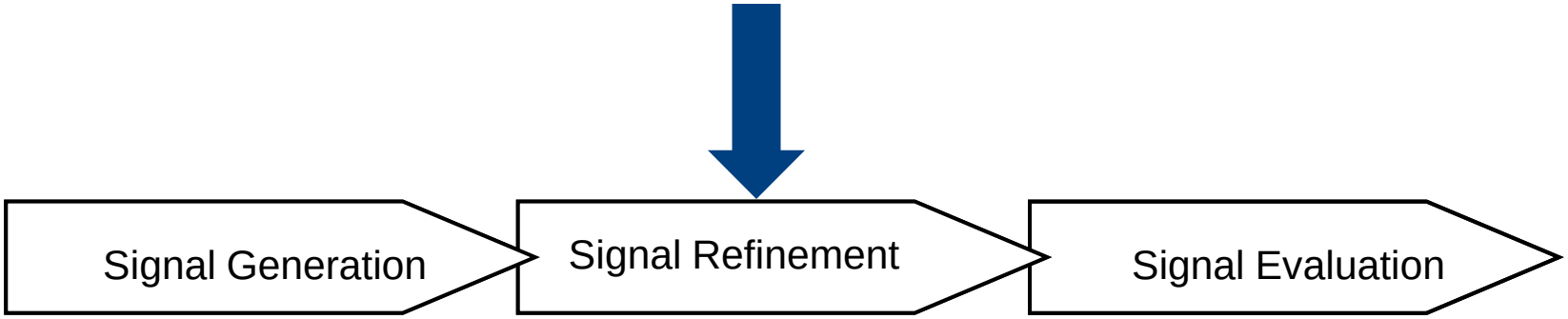
Newly marketed product

Define exposures, outcomes, etc

- **FDA: Selects product for surveillance**
- **6 mo prior to desired start**
- **Planning team:**
  - **Which outcomes?**
  - **Post-exposure time window?**
  - **Who is eligible?**
  - **Comparators?**
  - **Which confounders?**
  - **Which design?**
  - **Plan for promptly evaluating signals?**

PROMPT Outcome selection

- occurs in association with several other medical products of that type (e.g., acute liver injury for drugs; febrile seizures for vaccines) or another product in the class and is thus of general interest or
- reason to suspect that that product in particular might increase the risk of that HOI, for example because of a signal identified in pre-approval animal studies or clinical trials



- Signal refinement is a process for evaluating the magnitude and clinical significance of a suspected association

Standard outcome algorithms

GI bleeding
Pancreatitis
Premature delivery
Pulmonary Fibrosis
Hypertensive crisis
Agranulocytosis
Aplastic Anemia
Bronchospasm
CVA
Venous Thromboembolism
Hemorrhagic CVA
Ischemic CVA
Neutropenia
Bell's Palsy
Spontaneous abortion/Stillbirth
Acute Respiratory Failure
Sepsis
Deafness
Thrombotic thrombocytopenic purpura
Systemic lupus erythematosis
Inflammatory Bowel Disease
Juvenile RA
Tuberculosis
Erythema multiforme major
Idiopathic thrombocytopenic purpura
Thrombocytopenia
Henoch Schonlein purpura
Peripheral neuropathy
Guillan-Barre syndrome
Tendon rupture
Seizure, febrile
Suicide
Valvulopathy
Hip fracture
Pulmonary hypertension
Rhabdomyolysis
Sudden cardiac death
Diabetes

Standard Outcome Definitions:

Outcome	Algorithm	Rationale	Reference
Acute Ischemic Stroke	**Recommended Primary**: 434, 436 in first position of a hospital claim	Some algorithms also included 433.x1 and excluded 434.x0 (see Recommended Secondary), however 433.x1 may also have low PPV and the PPV for 434 (without exclusion) in first position is good (>85%). PPV diminishes slightly when any position, or when community vs tertiary care.	22262598 12105309
	Recommended Secondary: 433.x1, 434 (excluding 434.x0), 436 in first position of a hospital claim	Algorithm that included 433.x1, 434 (excluding 434.x0), and 436 performed well. 433 (other than 433.x0) had very low PPV. One study found 433.x1 PPV=71%	22262598 12364739
	Also Observed (but not recommended): 433, 434, 436 in first position	433 had very low PPV . 433.x0 PPV was 2%, 433.x1 PPV was only 20%	9707200

PROMPT Cohort selection

- Exclude prior history of event?
- Separate cohorts for each product indication?
- Separate cohorts for individuals with major risk factors?
- High priority subgroups

Standard cohort algorithms

- Persons with coronary artery disease
- Persons with mood disorders
- Persons with end-stage renal disease
- Hypertensives
- Smokers
- Asthmatics
- Persons with dementia
- Persons who received fluoroquinolones for post-exposure prophylaxis
- First responders
- Nursing home residents
- Pregnant women
- Live births
- Premature babies
- Persons at high risk for influenza complications
- Immunocompromised persons
- Type 1 diabetics
- Type 2 diabetics
- Obese persons

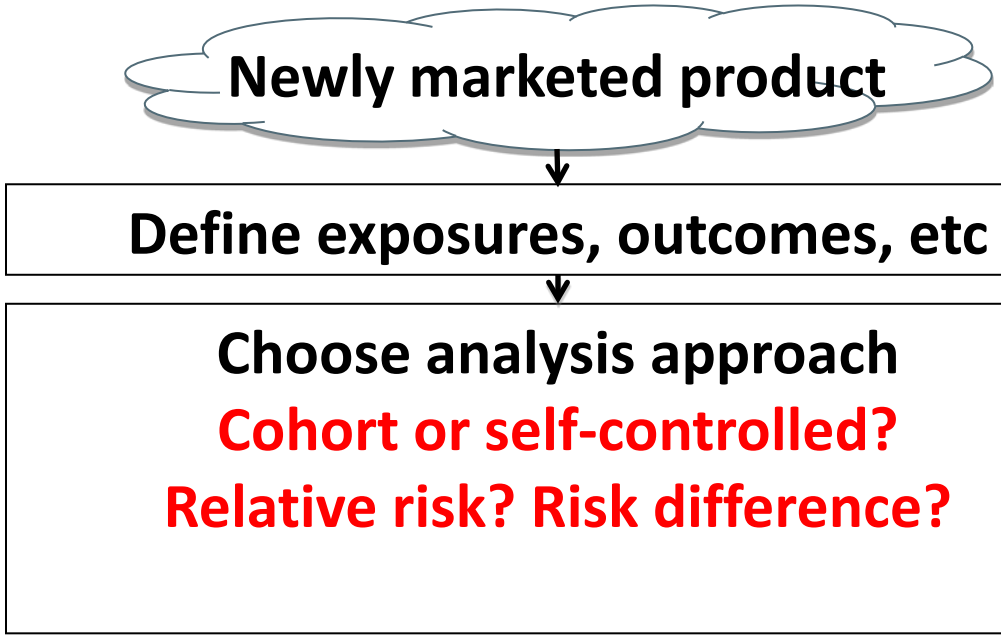
PROMPT Core confounder definitions

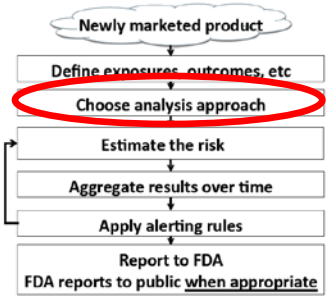
Demographics
Age
Sex
Calendar time*
Data Partner*
Healthcare utilization in baseline period
of visits to emergency departments
of ambulatory visits
of hospitalizations
of distinct drugs ordered/dispensed
of prescriptions ordered/dispensed
Lifestyle Factors
Smoking**, per algorithm developed by the “15 Cohorts” workgroup
Body mass index**[i], if available in the common data model; otherwise, per algorithm developed by the “15 Cohorts” workgroup
Combined Charlson-Elixhauser comorbidity index

* Requires special consideration given sequential analyses

** Discreetly-captured data field not currently in the Mini Sentinel Common Data Model, therefore alternate diagnosis-based algorithm suggested

PROMPT surveillance: how





What affects the choice? Exposure-outcome characteristics

Table 1. Scenario characteristics inherent to the specific exposure-outcome pair (i.e., scenario) that might affect design and analytic choice								
Exposure characteristics			**Characteristics of the (potential) exposure-HOI link**				**HOI characteristics**	
Background frequency of use in population	**Utilization trend in population**	**Use pattern**	**Onset of exposure risk window**	**Duration of exposure risk window**	**Strength of confounding**		**Background frequency**	**Expected degree of onset misclassification**
					Between person	**Within person**		
More frequent	Uniform	Short-term (including intermittent)	Immediate	Short	Negligible	Negligible	Infrequent	Negligible (e.g., HOI is mortality captured by vital statistics)
Less frequent	Changing (increasing, decreasing, cyclical)	Long-term	Short	Long	Needs to be addressed	Needs to be addressed	Rare	Pertinent (e.g., cancer)

Additional characteristics that might affect design and analytic choice

Effect measure of interest	Number of comparison groups	Comparison exposure
Difference measure	One	Active comparator
Relative measure	Multiple	Truly unexposed

PROMPT Module Selection Tool

- MS Taxonomy project aimed at "pre-thinking" major design and analysis considerations
  - Outlined methodological decisions in routine monitoring
  - Identified methodological options at each decision node
  - Determined the scenarios characteristics that might influence the decisions
  - Mapped scenario characteristics to recommended options
- Developed interactive tool to expedite decision-making process for routine monitoring

PROMPT Analysis Modules

Overview: Modular approach to drug safety monitoring in a distributed database system

- Build pre-programmed modules that can be quickly activated to monitor the use and safety effects of new and existing drugs
- Construct an analytic dataset based on pre-specified inputs:
  - Population eligibility
  - Outcome, exposure/comparator, and confounder definitions
- Describe the population of exposed and comparators
- Estimate adjusted safety effects across data partners
- Modules can be run once as single analyses or conducted repeatedly over time as data are refreshed and uptake occurs using sequential testing methods and pre-specified inputs:
  - Overall Type 1 (false positive) error to control across multiple tests
  - Frequency of testing and shape of signaling threshold over time
  - Maximum sample size after which surveillance will stop if no signal

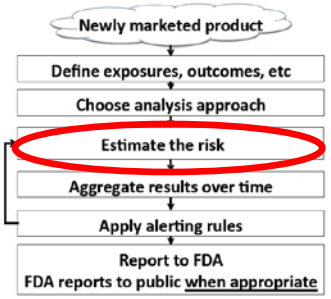
Some Details: Modular approach to drug safety monitoring in a distributed database system

- Validated programming code
- Can be run asynchronously across data partners as data get refreshed while preserving data privacy
- Methods involve standard epidemiologic designs and statistical methods
  - Confounding adjustment via a self-controlled design, PS matching, regression, or inverse weighting approaches
- Can estimate difference and ratio measures (rate or risk)
- Addresses heterogeneity across data partners
- Can flexibly employ a variety of sequential designs and analyses
  - Frequency of sequential analyses
  - Signaling rules for alerting a difference in risk between groups over time

Current Status: Modular approach to drug safety monitoring in a distributed database system

- Version 1 of code has been developed and tested in the MSDD
- Code development was conducted using several example pairs where association was deemed to be 'known':
  - True positive drug-event pair: ACEis and angioedema
  - True negative drug-event pair: clindamycin and AMI
  - True positive vaccine-event pair: MMRV and fever/seizure
- Version 1 of module user's manuals have been written
  - Includes needed module inputs and resulting standardized output
  - Describes the epidemiological design and statistical methods employed
- Version 1 of surveillance reports have been created
- Next steps: further testing and enhancement of code, manual and reports

PROMPT surveillance: estimate risk



Newly marketed product

Define exposures, outcomes, etc

Choose analysis approach

Estimate the risk

Module 1	Module 2	Module 3	Module 4
Self-controlled design	Exposure matching by propensity score (cohort design)	Regression (cohort design)	IPTW regression (cohort design)

Self-controlled design module (PROMPT 1)

- Variant of the self-controlled case series
- Utilizes cases (those who experience an adverse event) only
- Compares risk in exposed and comparator time windows within the same person
- Time-fixed confounders are implicitly controlled
- Future version will allow adjustment for time-varying confounders
- (Sequential) test is based on a LRT statistic comparing observed versus expected event counts
- Sequential boundaries extend maxSPRT method
  - Flat boundary; can delay 1st analysis, then continuous subsequent tests

Lisinopril-angioedema

Report date: 1/31/2014

Self-controlled group sequential analysis

Last exposure: 7/31/2013

Test no. 5

Cumulative exposed: 71,892

Sequential analysis history and results

Tracking		New events		Cumulative				Risk estimates		Hypothesis-testing statistics and results				
Test #	Most recent batch(es) included	No. of new events in risk interval ("cases")	No. of new events in control interval ("con-trols")	No. of exposed patients	No. of events in risk interval ("cases")	No. of events in control interval ("con-trols")	Expec-ted no. of cases	Relative risk	Risk differ-ence	Log likeli-hood ratio test statistic	Target alpha to spend	Actual alpha spent	No. of cases needed to reject H0 (CV)	H0 rejected ?
1														
2														
3														
4														
5														

Date of last analysis: 5/21/2013

PS matching module (PROMPT 2)

- First (of three) cohort approaches (e.g., new user design)
- Utilize individual-level data that remain at each data partner to
  - Estimate a PS (based on pre-specified confounders or using hd-PS)
  - Match exposed to unexposed patients using the PS (fixed matching ratio)
  - Evaluate diagnostics
- Minimal data combined for central analysis at MSOC
- Can compute HR, RR, RD comparing exposed and comparators, stratified by data partner
- Future version will allow disease risk score matching
- (Sequential) test is based on a LRT statistic comparing observed versus expected event counts
- Sequential boundaries extend maxSPRT method
  - Flat boundary; can delay 1st analysis, then continuous subsequent tests

PS Matching Dataset Creation Capabilities

- Substantial flexibility in defining exposures and outcomes, exposure windows, washout period, minimum exposures, blackout periods, etc.
  - Use enrollment data to reconcile overlaps and gaps; define continuous enrollment periods
  - Create continuous exposure periods, incorporating stockpiling
  - Identify incident exposure episodes and outcomes
  - Can restrict cohort based on eligibility criteria
  - Identifies and defines a wide range of core confounders (demographics, healthcare utilization, and comorbid conditions)

Inputs for Prospective Routine Observational Monitoring Program Tool: cohort matching program

ELIGIBILITY INFORMATION

- **Enrollment gap:** specifies the number of days bridged between two consecutive enrollment periods to create a single continuous enrollment period.

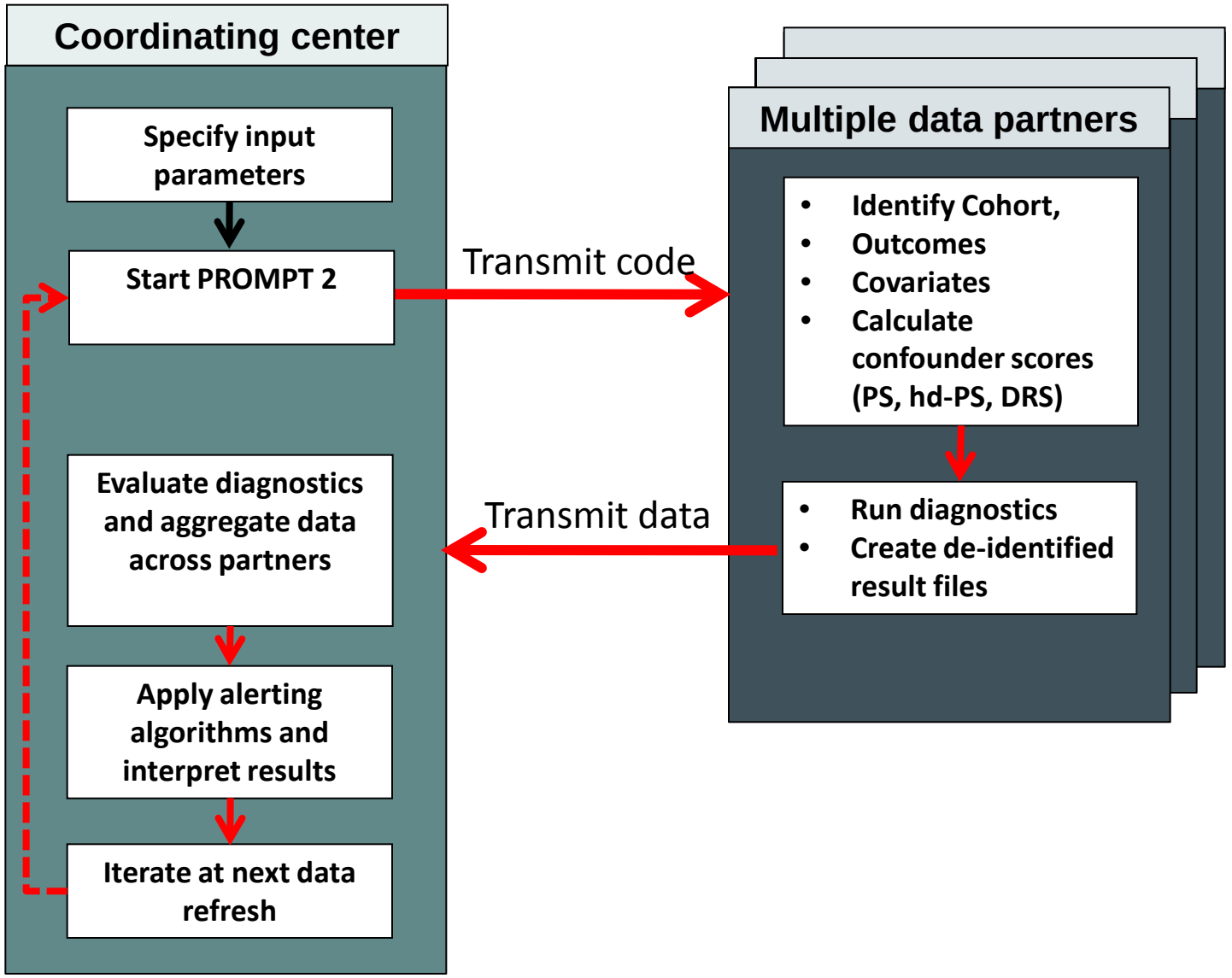
- **Inclusion/exclusion conditions:** defined by creating a SAS dataset with codes defining the inclusion or exclusion of conditions(s) of interest.

EXPOSURE INFORMATION

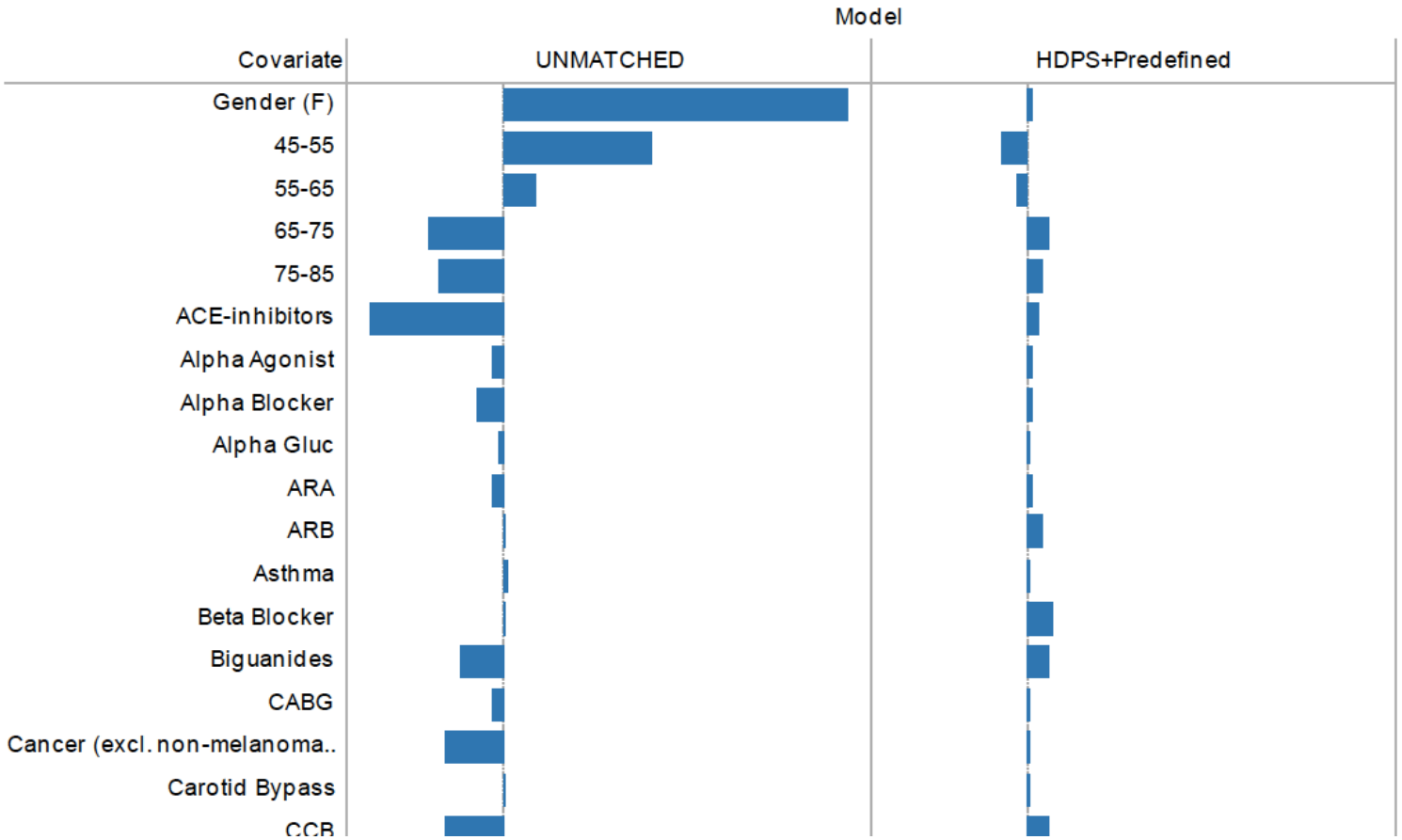
- **Medical product of interest:** defined by creating a SAS dataset with codes (i.e., NDCs or CPTs) to identify the product of interest.

- **Comparator of interest:** defined by creating a SAS dataset with codes (i.e., NDCs or CPTs) to identify the comparator product of interest.

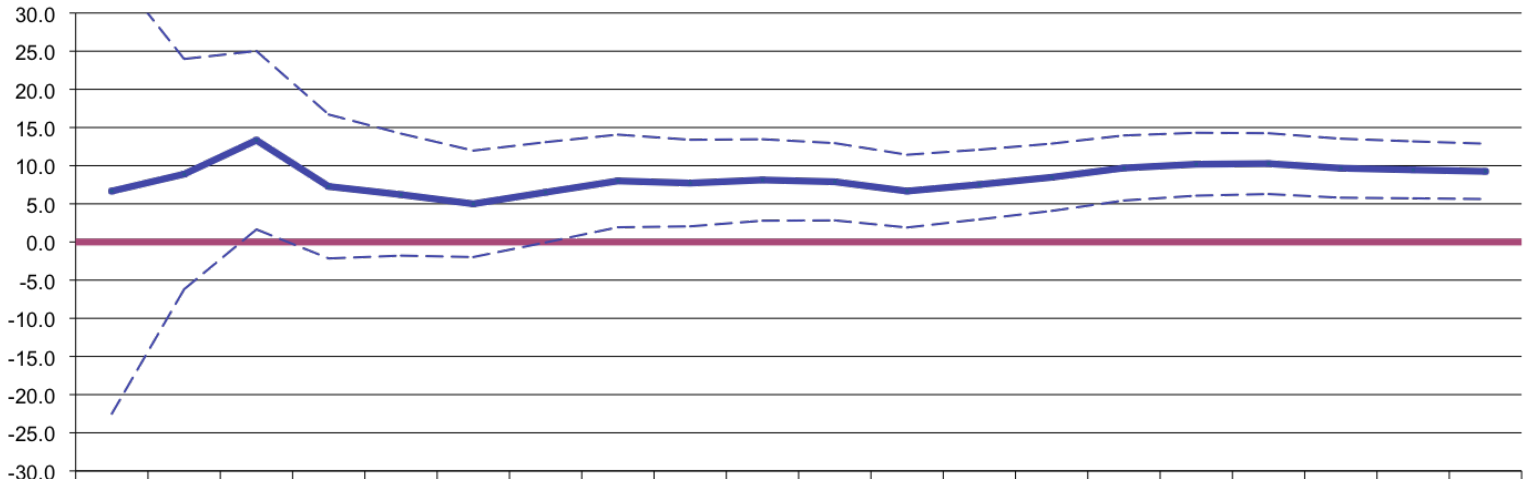
PS Matching Module in detail



Diagnostics: Balance before/after matching

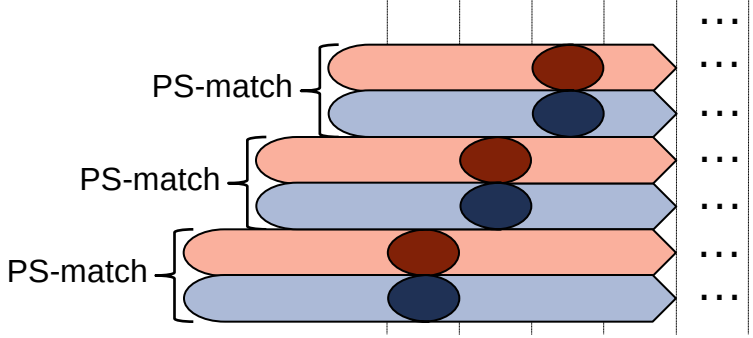


PS Module Results over time



Rate difference
(per 1,000 person-years)

	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



Regression module (PROMPT 3)

- A second cohort data approach (e.g., new user design)
- Individual-level data remain at each data partner
- De-identified data are then combined for central analysis at MSOC
- Can fit any generalized linear model of interest
  - Logistic regression to estimate an OR
  - Poisson regression to estimate a RR (and incorporate person-time data)
  - Linear regression to estimate a RD
- (Sequential) test is based on a score statistic
- Signaling boundaries leverage and extend RCT group sequential methods (unifying family by Kittleson et al.)
  - Allows flexible boundary shape specification (O'Brien-Fleming, Pocock, etc.)
  - Can customize testing plan (any continuous or group sequential plan)
  - Uses exact method boundary formulation (vs large sample assumptions)

Example Individual-level Dataset that remains at each Data Partner

StudyID	Age	Sex	Smoker	Weight	Height	Flu Vaccine	…
1	28	F	Current	135	5’6”	Yes	
2	45	M	Quit	190	6’0”	No	
…							
100,000	51	M	Never	180	5’10”	Yes	

Example of combined aggregated data sent to MSOC: event counts by strata

Site	Age Cat	Sex	Flu Vaccine	Events	N
A	25-30	F	Yes	10	1000
A	25-30	F	No	15	600
A	25-30	M	Yes	4	2000
A	25-30	M	No	10	1000
…					
A	60-65	M	No	55	5000
B	25-30	F	Yes	25	10000
B	25-30	F	No	88	8000
…					

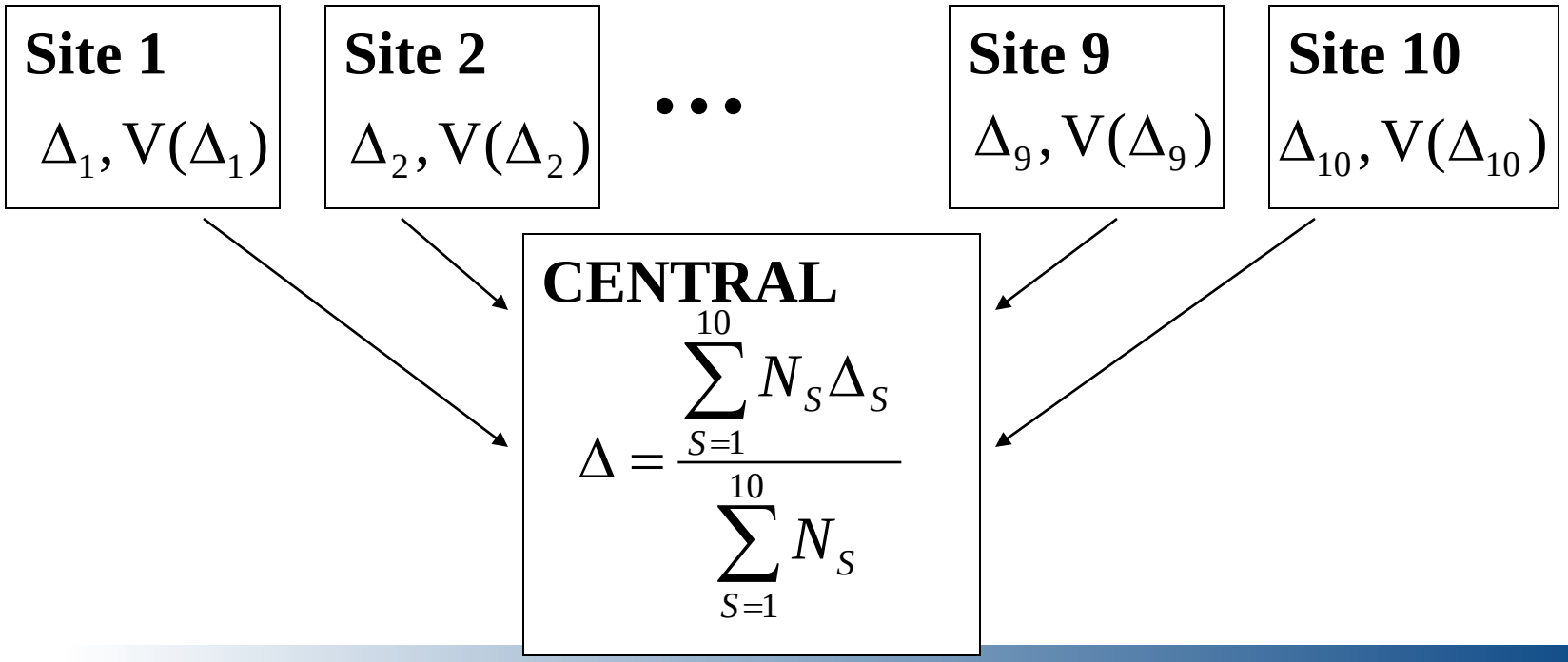
IPTW regression module (PROMPT 4)

- A third cohort approach (e.g., new user design)
- Utilizes individual-level data that remain at each data partner to
  - Estimate a PS based on pre-specified confounders
  - Estimate a RD using linear regression, inverse weighted by the PS
- Summary statistics are combined across data partners for analysis
- Acknowledges site heterogeneity by computing a stratified RD estimate that incorporates variability in propensity score models
- (Sequential) test is based on a Wald test statistic
- Sequential boundaries leverage and extend RCT methods
  - Allows flexible boundary shape specification (O'Brien-Fleming, Pocock, etc.)
  - Can customize testing plan (any continuous or group sequential plan)
  - Uses exact method boundary formulation (vs. large sample assumptions)

IPTW regression module

Involves a stratified IPTW risk difference

- Construct site-specific propensity scores (logistic regression)
- Calculate site-specific IPTW risk difference Δ_S& variance $V(\Delta_S)$ (Lunceford & Davidian 2004); send with N_s to a central location



IPTW regression module

Uses a non-parametric permutation approach for rare events

- Fix outcomes and confounders and permute exposure w/in site
- Sites also send permuted datasets $\left\{\left(\Delta_S^{(1)}, \mathrm{V}(\Delta_S^{(1)})\right), \ldots, \left(\Delta_S^{(P)}, \mathrm{V}(\Delta_S^{(P)})\right)\right\}$

Site 1

$$N_1, \left(\Delta_1, \mathrm{V}(\Delta_1)\right),$$
$$\left\{\left(\Delta_1^{(1)}, \mathrm{V}(\Delta_1^{(1)})\right), \ldots, \left(\Delta_1^{(P)}, \mathrm{V}(\Delta_1^{(P)})\right)\right\}$$

• • •

Site 8

$$N_8, \left(\Delta_8, \mathrm{V}(\Delta_8)\right),$$
$$\left\{\left(\Delta_8^{(1)}, \mathrm{V}(\Delta_8^{(1)})\right), \ldots, \left(\Delta_8^{(P)}, \mathrm{V}(\Delta_8^{(P)})\right)\right\}$$

CENTRAL

Overall adjusted risk difference

Distribution of permuted risk difference under H_0

Repeat for each analysis time t=1, 2…T)

Use unifying family (Kittleson) to derive stopping boundaries

Example IPTW module reports

Table 1: Demographics of Population by Exposure Group

	Total	MMR+V	MMRV
Total, N(Row%)	34823 (100.0)	17502 (50.3)	17321 (49.7)
Age, N(Col%)			
11m-12m	17728 (50.9)	10089 (57.6)	7639 (44.1)
13m-14m	7038 (20.2)	3267 (18.7)	3771 (21.8)
15m-16m	6171 (17.7)	2434 (13.9)	3737 (21.6)
17m-19m	2681 (7.7)	1143 (6.5)	1538 (8.9)
20m-23m	1205 (3.5)	569 (3.3)	636 (3.7)
Sex, N(Col%)			
Male	17798 (51.1)	9040 (51.7)	8758 (50.6)
Female	17025 (48.9)	8462 (48.3)	8563 (49.4)
Site, N(Col%)			
4	5090 (14.6)	4981 (28.5)	109 (0.6)
15	18353 (52.7)	4175 (23.9)	14178 (81.9)
16	11380 (32.7)	8346 (47.7)	3034 (17.5)

Example IPTW module reports

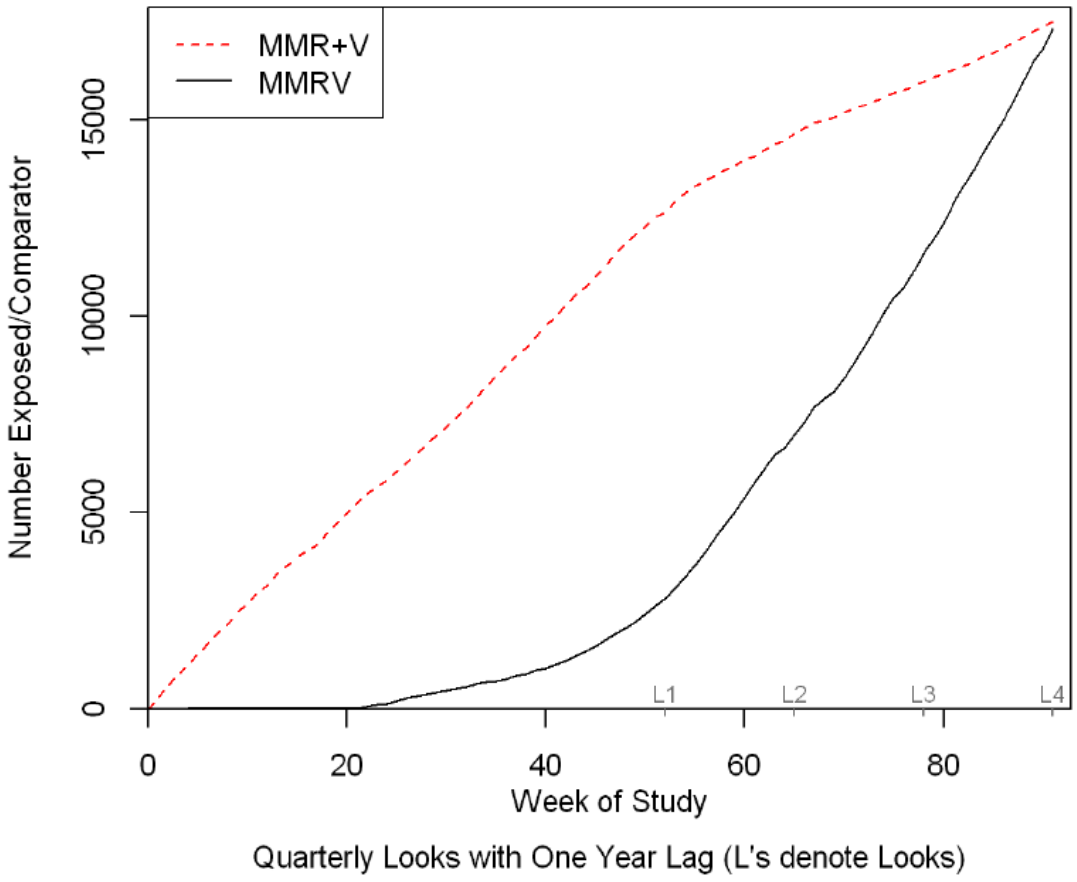


Figure 1: Total uptake of MMRV and MMR+V over Time at Look 4

Example IPTW module reports

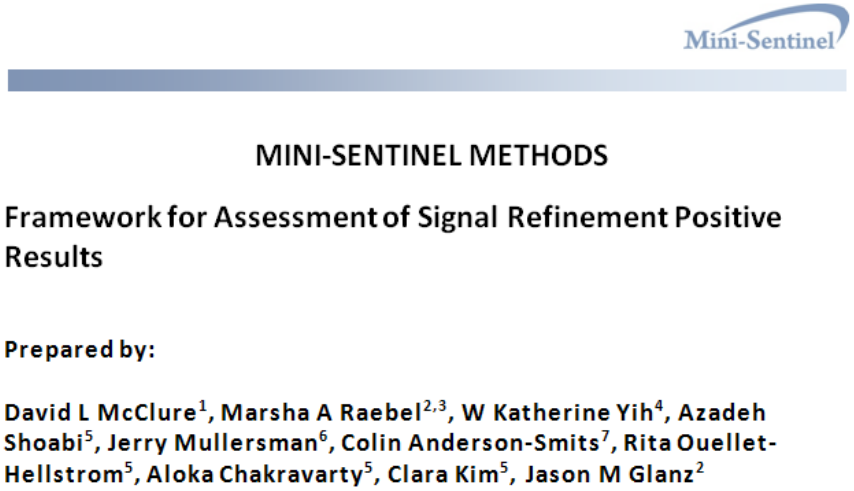
Table 2: Results of adjusted sequential monitoring using stratified GS IPTW comparing MMR+V to MMRV on outcome Seizure

Look:	Days	MMR+V N	MMR+V Out(%Out)	MMRV N	MMRV Out(%Out)	MMR+V Adj %Out	MMRV Adj %Out	Adj RD*	IPTW Test	Boundary	Error Spent	Signal
1:	364	12652	5(0.040)	2796	5(0.179)	0.043	0.074	0.031	0.794	1.297	0.028	No
2:	455	14633	7(0.048)	6970	10(0.143)	0.045	0.088	0.043	1.261	2.043	0.032	No
3:	546	15968	7(0.044)	11577	14(0.121)	0.036	0.086	0.051	1.790	2.074	0.032	No
4:	637	17502	7(0.040)	17321	18(0.104)	0.028	0.080	0.052	2.235	2.069	0.032	Yes

*Adjusted stratified risk difference model applied using GS IPTW with sequential monitoring boundaries based on permutations.
Covariates Included: Age, Sex, and indicator for each look within site strata.
Abbreviations: IPTW=Inverse Probability of Treatment Weighting, Out=Num. of outcomes, %Out=Incidence rate of outcome within look and covariate category, Adj=Adjusted, RD=Risk Difference, Adj %Out= Adjusted estimated %Out from stratified IPTW model for a given exposure group, Adj RD= MMRV Adj %Out - MMR+V Adj %Out = stratified IPTW adjusted RD per 100, IPTW Test = Adj RD/Standard Error(Adj RD), and Boundary = Sequential Boundary to compare the IPTW Test Estimate.
Sequential P-Value at Signal: 0.0319

What happens when we find something?

- Prompt, pre-planned product-specific assessment of positive signal (or in the absence of signal)
- Examples of post-monitoring follow-up activities:
  - Data checks, analytic code checks
  - Subgroup analyses
  - Adjust for additional confounders
  - Test against other comparators
  - Vary population, O, or E definitions
  - 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

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Example report: demographics over time

Table A.1: Outcome Counts and Incidence Rates by Look and Covariate Strata

	Look 1	Look 2	Look 3	Look 4
Total, Out(%Out)	10 (0.065)	17 (0.079)	21 (0.076)	25 (0.072)
Age, Out(%Out)				
11m-12m	3 (0.036)	6 (0.053)	7 (0.050)	9 (0.051)
13m-14m	3 (0.098)	4 (0.094)	5 (0.090)	5 (0.071)
15m-16m	2 (0.079)	2 (0.054)	2 (0.041)	3 (0.049)
17m-19m	1 (0.093)	3 (0.192)	4 (0.195)	4 (0.149)
20m-23m	1 (0.201)	2 (0.275)	3 (0.329)	4 (0.332)
Sex, Out(%Out)				
Male	4 (0.051)	8 (0.072)	10 (0.071)	12 (0.067)
Female	6 (0.080)	9 (0.085)	11 (0.082)	13 (0.076)
Site, Out(%Out)				
4	1 (0.035)	1 (0.028)	1 (0.023)	1 (0.020)
15	7 (0.109)	10 (0.100)	13 (0.095)	17 (0.093)
16	2 (0.032)	6 (0.075)	7 (0.073)	7 (0.062)

*Abbreviations: Out=Num. of outcomes and %Out=Incidence rate of outcome within look and covariate stratum.

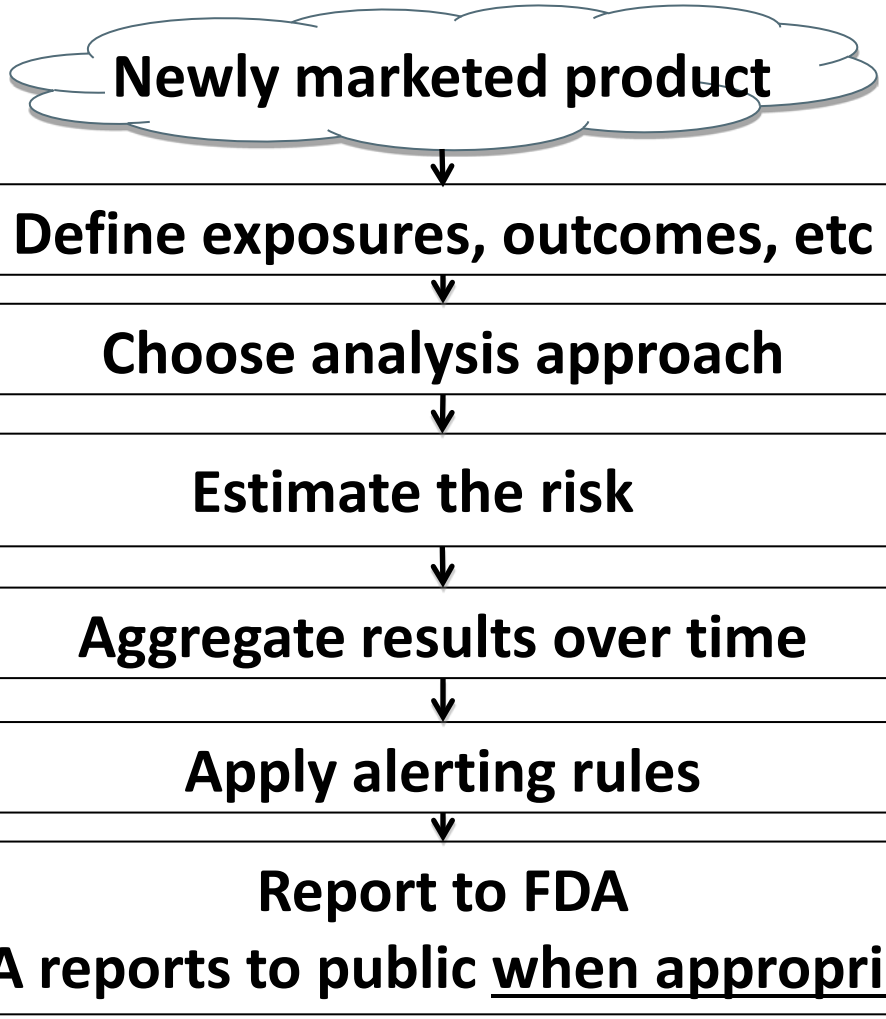
Example report: surveillance results by site

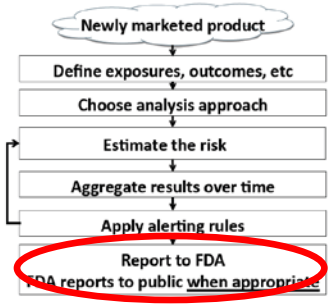
Table A.5: Current analysis comparing MMR+V to MMRV on outcome Seizure by site

Site	MMR+V N	MMR+V Out(%Out)	MMRV N	MMRV Out(%Out)	MMR+V Adj %Out	MMRV Adj %Out	Adj RD*	IPTW Test
4	4981	1(0.020)	109	0(0.000)	0.020	0.000	-0.020	-1.000
15	4175	2(0.048)	14178	15(0.106)	0.020	0.120	0.100	2.753
16	8346	4(0.048)	3034	3(0.099)	0.046	0.052	0.006	0.162

*Adjusted risk difference model applied using IPTW(no Sequential).
Covariates Included: Age, Sex, and indicator for each look within site strata.
Abbreviations: IPTW=Inverse Probability of Treatment Weighting, Out=Num. of outcomes, %Out=Incidence rate of outcome within look and covariate category, Adj=Adjusted, RD=Risk Difference, Adj %Out= Adjusted estimated %Out from stratified IPTW model for a given exposure group, Adj RD= MMRV Adj %Out - MMR+V Adj %Out = stratified IPTW adjusted RD per 100, and IPTW Test = Adj RD/Standard Error(Adj RD)

PROMPT surveillance: reporting





Information from Mini Sentinel's PROMPT is used to complement other FDA data to help inform regulatory action

Thank You!

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ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Roundtable on Active Medical Product Surveillance

An Overview of the Design and Implementation of FDA's Prospective Routine Observational Monitoring Program Tools for Safety Surveillance

Jennifer Nelson, Group Health Research Institute and University of Washington

Elizabeth Chrischilles, University of Iowa Department of Epidemiology

Monday, September 16, 2013