Brookings Roundtable on Active Medical Product 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
Housekeeping

- To minimize feedback, please confirm that the microphone on your telephone is muted.
- To mute your phone, press the mute button or ‘*6’. (To un-mute, press ‘*7’)
- There will be opportunities for questions and discussion at the end of today’s presentations. Please use the Q & A tab on the top of your screen to submit your questions into the queue at any point and we will call upon you to state your question.
- Call the Level 3 Conferencing at 1-888-447-1119 with technical problems.
Brookings Roundtable on Active Medical Product Surveillance


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Monday, September 16, 2013
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

Newly marketed product

1. Define exposures, outcomes, etc
2. Choose analysis approach
3. Estimate the risk
4. Aggregate results over time
5. Apply alerting rules
6. Report to FDA
   - FDA reports to public when appropriate
PROMPT surveillance: who, what, when

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:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Algorithm</th>
<th>Rationale</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Ischemic Stroke</td>
<td><strong>Recommended Primary:</strong> 434, 436 in first position of a hospital claim</td>
<td>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 (&gt;85%). PPV diminishes slightly when any position, or when community vs tertiary care.</td>
<td>22262598 12105309</td>
</tr>
<tr>
<td></td>
<td><strong>Recommended Secondary:</strong> 433.x1, 434 (excluding 434.x0), 436 in first position of a hospital claim</td>
<td>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%</td>
<td>22262598 12364739</td>
</tr>
<tr>
<td></td>
<td>Also Observed (but not recommended): 433, 434, 436 in first position</td>
<td>433 had very low PPV. 433.x0 PPV was 2%, 433.x1 PPV was only 20%</td>
<td>9707200</td>
</tr>
</tbody>
</table>
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
- Asthmetics
- 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

<table>
<thead>
<tr>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Calendar time*</td>
</tr>
<tr>
<td>Data Partner*</td>
</tr>
</tbody>
</table>

### Healthcare utilization in baseline period

<table>
<thead>
<tr>
<th># of visits to emergency departments</th>
</tr>
</thead>
<tbody>
<tr>
<td># of ambulatory visits</td>
</tr>
<tr>
<td># of hospitalizations</td>
</tr>
<tr>
<td># of distinct drugs ordered/dispensed</td>
</tr>
<tr>
<td># of prescriptions ordered/dispensed</td>
</tr>
</tbody>
</table>

### Lifestyle Factors

<table>
<thead>
<tr>
<th>Smoking**, per algorithm developed by the “15 Cohorts” workgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index**, if available in the common data model; otherwise, per algorithm developed by the “15 Cohorts” workgroup</td>
</tr>
<tr>
<td>Combined Charlson-Elixhauser comorbidity index</td>
</tr>
</tbody>
</table>

* 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
Define exposures, outcomes, etc

Choose analysis approach
Cohort or self-controlled? Relative risk? Risk difference?

Newly marketed product
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

<table>
<thead>
<tr>
<th>Exposure characteristics</th>
<th>Characteristics of the (potential) exposure-HOI link</th>
<th>HOI characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset of exposure risk window</td>
<td>Strength of confounding</td>
</tr>
<tr>
<td></td>
<td>Duration of exposure risk window</td>
<td>Between person</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Background frequency</td>
</tr>
<tr>
<td>Background frequency of use in population</td>
<td>Utilization trend in population</td>
<td>Use pattern</td>
</tr>
<tr>
<td>More frequent</td>
<td>Uniform</td>
<td>Short-term (including intermittent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term</td>
</tr>
<tr>
<td>Less frequent</td>
<td>Changing (increasing, decreasing, cyclical)</td>
<td></td>
</tr>
</tbody>
</table>
Additional characteristics that might affect design and analytic choice

<table>
<thead>
<tr>
<th>Effect measure of interest</th>
<th>Number of comparison groups</th>
<th>Comparison exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference measure</td>
<td>One</td>
<td>Active comparator</td>
</tr>
<tr>
<td>Relative measure</td>
<td>Multiple</td>
<td>Truly unexposed</td>
</tr>
</tbody>
</table>
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
Self-controlled design

Module 2
Exposure matching by propensity score (cohort design)

Module 3
Regression (cohort design)

Module 4
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

Cumulative exposed: 71,892

---

**Sequential analysis history and results**

<table>
<thead>
<tr>
<th>Test #</th>
<th>Most recent batch(es) included</th>
<th>New events</th>
<th>Cumulative</th>
<th>Risk estimates</th>
<th>Hypothesis-testing statistics and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of new events in risk interval (“cases”)</td>
<td>No. of new events in control interval (“controls”)</td>
<td>No. of events in risk interval (“cases”)</td>
<td>No. of events in control interval (“controls”)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Coordinating center

- Specify input parameters
- Start PROMPT 2
- Evaluate diagnostics and aggregate data across partners
- Apply alerting algorithms and interpret results
- Iterate at next data refresh

Multiple data partners

- Identify Cohort, Outcomes, Covariates
- Calculate confounder scores (PS, hd-PS, DRS)
- Run diagnostics
- Create de-identified result files

Transmit code
Transmit data
Iterate at next data refresh
Diagnostics: Balance before/after matching

<table>
<thead>
<tr>
<th>Covariate</th>
<th>UNMATCHED</th>
<th>HDPS+Predefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Gluc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer (excl. non-melanoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid Bypass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PS Module Results over time

Rate difference (per 1,000 person-years)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower 95% confidence interval</td>
<td>-22.50</td>
<td>-6.20</td>
<td>1.65</td>
<td>-2.16</td>
<td>-1.79</td>
<td>-1.97</td>
<td>-0.06</td>
<td>1.93</td>
<td>2.05</td>
<td>2.79</td>
<td>2.83</td>
<td>1.90</td>
<td>2.96</td>
<td>4.07</td>
<td>5.43</td>
<td>6.07</td>
<td>6.28</td>
<td>5.80</td>
<td>5.72</td>
<td>5.62</td>
</tr>
</tbody>
</table>

Cumulative events: monitoring drug
- 3  8  15  18  22  25  33  40  45  51  56  58  65  73  82  89  95  99  103  108
- 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
- 150  450  750  1100  1450  1800  2150  2500  2850  3200  3550  3900  4250  4600  4950  5300  5650  6000  6350  6700

PS-match

info@mini-sentinel.org
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

<table>
<thead>
<tr>
<th>StudyID</th>
<th>Age</th>
<th>Sex</th>
<th>Smoker</th>
<th>Weight</th>
<th>Height</th>
<th>Flu Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>F</td>
<td>Current</td>
<td>135</td>
<td>5’6”</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>Quit</td>
<td>190</td>
<td>6’0”</td>
<td>No</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000</td>
<td>51</td>
<td>M</td>
<td>Never</td>
<td>180</td>
<td>5’10”</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Example of combined aggregated data sent to MSOC: event counts by strata

<table>
<thead>
<tr>
<th>Site</th>
<th>Age Cat</th>
<th>Sex</th>
<th>Flu Vaccine</th>
<th>Events</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25-30</td>
<td>F</td>
<td>Yes</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>A</td>
<td>25-30</td>
<td>F</td>
<td>No</td>
<td>15</td>
<td>600</td>
</tr>
<tr>
<td>A</td>
<td>25-30</td>
<td>M</td>
<td>Yes</td>
<td>4</td>
<td>2000</td>
</tr>
<tr>
<td>A</td>
<td>25-30</td>
<td>M</td>
<td>No</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>60-65</td>
<td>M</td>
<td>No</td>
<td>55</td>
<td>5000</td>
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<tr>
<td>B</td>
<td>25-30</td>
<td>F</td>
<td>Yes</td>
<td>25</td>
<td>10000</td>
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<tr>
<td>B</td>
<td>25-30</td>
<td>F</td>
<td>No</td>
<td>88</td>
<td>8000</td>
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<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 $\Delta_S$ & variance $V(\Delta_S)$ (Lunceford & Davidian 2004); send with $N_S$ to a central location

\[
\Delta = \frac{\sum_{S=1}^{10} N_S \Delta_S}{\sum_{S=1}^{10} N_S}
\]
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 \( \left\{ \left( \Delta^{(1)}_s, V(\Delta^{(1)}_s) \right), \ldots, \left( \Delta^{(P)}_s, V(\Delta^{(P)}_s) \right) \right\} \)

Site 1

\[ N_1, \left( \Delta_1, V(\Delta_1) \right), \left\{ \left( \Delta^{(1)}_1, V(\Delta^{(1)}_1) \right), \ldots, \left( \Delta^{(P)}_1, V(\Delta^{(P)}_1) \right) \right\} \]

Site 8

\[ N_8, \left( \Delta_8, V(\Delta_8) \right), \left\{ \left( \Delta^{(1)}_8, V(\Delta^{(1)}_8) \right), \ldots, \left( \Delta^{(P)}_8, V(\Delta^{(P)}_8) \right) \right\} \]

CENTRAL

Overall adjusted risk difference

Distribution of permuted risk difference under \( H_0 \)

Repeat for each analysis time \( t=1, 2\ldots T \)

Use unifying family (Kittleson) to derive stopping boundaries
Example IPTW module reports

<table>
<thead>
<tr>
<th>Table 1: Demographics of Population by Exposure Group</th>
<th>Total</th>
<th>MMR+V</th>
<th>MMRV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, N(Row%)</td>
<td>34823 (100.0)</td>
<td>17502 (50.3)</td>
<td>17321 (49.7)</td>
</tr>
<tr>
<td>Age, N(Col%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11m-12m</td>
<td>17728 (50.9)</td>
<td>10089 (57.6)</td>
<td>7639 (44.1)</td>
</tr>
<tr>
<td>13m-14m</td>
<td>7038 (20.2)</td>
<td>3267 (18.7)</td>
<td>3771 (21.8)</td>
</tr>
<tr>
<td>15m-16m</td>
<td>6171 (17.7)</td>
<td>2434 (13.9)</td>
<td>3737 (21.6)</td>
</tr>
<tr>
<td>17m-19m</td>
<td>2681 (7.7)</td>
<td>1143 (6.5)</td>
<td>1538 (8.9)</td>
</tr>
<tr>
<td>20m-23m</td>
<td>1205 (3.5)</td>
<td>569 (3.3)</td>
<td>636 (3.7)</td>
</tr>
<tr>
<td>Sex, N(Col%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17798 (51.1)</td>
<td>9040 (51.7)</td>
<td>8758 (50.6)</td>
</tr>
<tr>
<td>Female</td>
<td>17025 (48.9)</td>
<td>8462 (48.3)</td>
<td>8563 (49.4)</td>
</tr>
<tr>
<td>Site, N(Col%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5090 (14.6)</td>
<td>4981 (28.5)</td>
<td>109 (0.6)</td>
</tr>
<tr>
<td>15</td>
<td>18353 (52.7)</td>
<td>4175 (23.9)</td>
<td>14178 (81.9)</td>
</tr>
<tr>
<td>16</td>
<td>11380 (32.7)</td>
<td>8346 (47.7)</td>
<td>3034 (17.5)</td>
</tr>
</tbody>
</table>
Example IPTW module reports

Figure 1: Total uptake of MMRV and MMR+V over Time at Look 4
Table 2: Results of adjusted sequential monitoring using stratified GS IPTW comparing MMR+V to MMRV on outcome Seizure

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

*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
Example report: demographics over time

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

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

*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

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

*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

Newly marketed product

- Define exposures, outcomes, etc
- Choose analysis approach
- Estimate the risk
- Aggregate results over time
- Apply alerting rules
- Report to FDA
  FDA reports to public when appropriate
Information from Mini Sentinel’s PROMPT is used to complement other FDA data to help inform regulatory action
Thank You!

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Brookings Roundtable on Active Medical Product Surveillance


Jennifer Nelson, Group Health Research Institute and University of Washington

Elizabeth Chrischilles, University of Iowa Department of Epidemiology

Monday, September 16, 2013