Brookings Roundtable on Active Medical Product Surveillance:

Developing a Taxonomy of Surveillance Methods for Medical Product Safety

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• Meghan Baker, Harvard Medical School, Harvard Pilgrim Healthcare Institute, and Brigham and Women’s Hospital

December 7, 2012
Taxonomy for monitoring methods within a medical product safety surveillance system

Joshua J Gagne
on behalf of the Taxonomy Work Group

Brookings Roundtable on Active Medical Product Surveillance
December 7, 2012
Overview

- Background
- Objectives
- Scenario characteristics
- Decision points and methods options
- Worked example
- Conclusions and future
Background
Background

- Many design and analytic methods are available for active medical product safety surveillance.
- Each method requires certain assumptions that may be tenable in some scenarios but not others.
  
  Note: I define “scenario” as a single exposure/outcome pair.
- No single method will perform well in all scenarios.
- Pre-thinking which methods are most suitable for which situations promotes collaborative, transparent, intelligible, and timely decision-making.
Overall project objectives

• Identify scenario characteristics that have implications for methodological decisions
• Characterize analytic methods suitable for signal refinement
• Map combinations of scenario characteristics to appropriate methods using structure decision table
• Evaluate the framework using FDA-relevant examples
• Develop interface and implementation guide
Scenario-method mapping

Characteristics defined by stakeholders
Exposure characteristics
Outcome characteristics
Characteristics of the link between exposure and outcome

Design options
Analysis options
Scenario-method mapping

Characteristics defined by stakeholders
Exposure characteristics
Outcome characteristics
Characteristics of the link between exposure and outcome

Design options
Analysis options
Scenario characteristics

- Characteristics defined by stakeholders

<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>
Scenario characteristics

- **Exposure characteristics**
  - Background frequency of use in population
  - Utilization trend in population
  - Use pattern

- **Health outcomes of interest (HOI) characteristics**
  - Background frequency
  - Expected degree of onset misclassification

- **Characteristics of the (potential) exposure-HOI link**
  - Onset of exposure risk window
  - Duration of exposure risk window
  - Strength of confounding (within- and between-person)
Scenario-method mapping

Characteristics defined by stakeholders
Exposure characteristics
Outcome characteristics
Characteristics of the link between exposure and outcome

Design options
Analysis options
Key design and analytic decision points

- Contrast

- Methods to address exposure time trend

- Methods to address confounding
  - Confounder summarization
  - Incorporation into estimation

- Estimation
Contrast

- Analyses always boil down to observed (counts, rates, etc) vs. expected comparisons (counts, rates, etc)

- Expected numbers can be estimated from the same individual or from other individuals
  - Within-person
    - i.e., self-controlled case series, case-crossover, and their variants
  - Between-person
    - i.e., cohort and related sampling strategies (case-control, case-cohort, etc.)
Methods to address exposure time trend

- Self-controlled approaches can sometimes be biased in the presence of a background trend in exposure
  - e.g., rapid increase in use of a new drug, seasonal variation in use of antibiotics

- Options:
  - Self-controlled case series
  - Case-time-control
  - Case-case-time-control
Methods to address baseline confounding

Confounder summary scores

- Safety surveillance often involves rare events and/or infrequent exposures
- Traditional adjustment approaches (e.g., covariate stratification and multivariable regression) are limited in these settings
- Confounder summary scores can incorporate many more covariates:
  - Propensity scores
  - Disease risk scores
Methods to address baseline confounding

Incorporation into estimation

- Confounder summary scores can be used in the same ways as multiple individual covariates

- Options
  - Stratification
  - Matching
  - Independent variable in outcome regression model
  - Weighting
Estimation

- Multiple models can be applied regardless of how covariates are summarized (or not) and incorporated into the analysis:
  - No outcome model (e.g., simple comparison of cumulative incidences or rates, stratified approaches such as Mantel-Haenszel)
  - Generalized linear models (e.g., logistic or Poisson regression)
  - Survival models (e.g., Cox proportional hazards model)
### Example 5: Rosuvastatin and rhabdomyolysis

**Characteristics determined by stakeholders/investigators**

| Effect measure(s) of interest | Both difference and ratio measures |
| Comparator(s)                | Other statins (excluding cerivastatin) |

**Exposure characteristics**

| Background frequency of use:     | More frequent |
| Utilization trend in population: | Changing (increasing) |
| Use pattern                     | Long-term    |

**Characteristics of the potential exposure-HOI link**

| Onset of exposure risk window: | Immediate |
| Duration of exposure risk window: | Long |
| Strength of confounding         |            |
| Between-person                  | Negligible (when compared to other statins) |
| Within-person                   | Negligible  |

**HOI Characteristics**

| Background frequency | Rare |
| Periodicity          | Once |
| Expected degree of onset misclassification | Negligible (within days) |
### Example: rosuvastatin and rhabdo

<table>
<thead>
<tr>
<th>Characteristics of the (potential) exposure contour</th>
<th>Characteristics inherent to the specific exposure monitoring scenarios</th>
<th>Characteristics determined by stakeholder/investigator</th>
<th>Exposure characteristics</th>
<th>Use characteristics</th>
<th>Background frequency trend in population</th>
<th>One comparator exposure</th>
<th>Number of comparator exposure groups</th>
<th>Comparison of interest</th>
<th>Effect measure difference measure</th>
<th>Number of exposure groups</th>
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</thead>
<tbody>
<tr>
<td>Short-term</td>
<td>Immediate Long</td>
<td>Short Long Short</td>
<td>Immediate Needs to be addressed Long Needs to be addressed</td>
<td>Needs to be addressed</td>
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Example: rosuvastatin and rhabdo

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<th>Onset of exposure risk window</th>
<th>Duration of exposure risk window</th>
<th>Strengh confound</th>
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</thead>
<tbody>
<tr>
<td>Difference measure</td>
<td>One</td>
<td>Active comparator</td>
<td>Infrequent</td>
<td>Changing (increasing, decreasing, cyclical)</td>
<td>Long-term</td>
<td>Immediate</td>
<td>Long</td>
<td>Needs to be addressed</td>
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Recommendation: Cohort design with or without confounder summarization via PS using a time-to-event model
Conclusion and future directions

- Many robust methods exist for surveillance activities and additional methods work is needed in key areas.
- Certain methodological decisions depend on factors outside of scenario characteristics (e.g., whether to match or stratify).
- Decisions often depend on nuanced clinical and epidemiologic input.
- Few combinations of methods can cover a majority of routine surveillance activities.
- Taxonomies for specific product types (e.g., devices, biologics, etc) can address additional nuance.
Key characteristics of monitoring setting Gagne et al PDS 2012

Module 1
Self-controlled case series
Parameters:
- Exposure time
- Trend adjustment
- ...

Maclure et al PDS 2012
Farrington et al...
Wang et al. Epidemiology 2011

Module 2
Cohort approach 1
Parameters:
- Score-based matching (PS, DRS)
- Fixed/variable ratio
- ...

Rassen et al AJE 2011, PDS 2012;
Schneeweiss et al. Epidemiol 2009; Glynn et al PDS 2012

Module 3
Cohort approach 2
Parameters:
- Minimally stratified
- Regression
- ...

Brown et al PDS 2009
Nelson et al PDS 2012;
Cook et al. PDS 2012

Aggregation of cumulating data over time
Schneeweiss et al. CPT 2011; Gagne et al. CPT 2012 in press

Applying alerting rules based on acceptable risk levels
Gagne et al. Epidemiology 2012
# Framework evaluation

## Taxonomy scenario characteristic selection table

**Framework evaluation**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Determined by stakeholder/investigator</th>
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<tr>
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<td></td>
<td>Use pattern</td>
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</table>

**Options:**
- difference measure
- active comparator
- more frequent
- uniform
- short-term (including intermittent)
- intermittent
- multiple
- truly unexposed
- less frequent
- changing (increase, decreasing, cyclical)
- long-term
- short-term
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