ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Roundtable on Active Medical Product Surveillance:

Developing a Taxonomy of Surveillance Methods for Medical Product Safety

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- Joshua Gagne, Brigham and Women's Hospital and Harvard Medical School
- Meghan Baker, Harvard Medical School, Harvard Pilgrim Healthcare Institute, and Brigham and Women's Hospital

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Taxonomy for monitoring methods within a medical product safety surveillance system

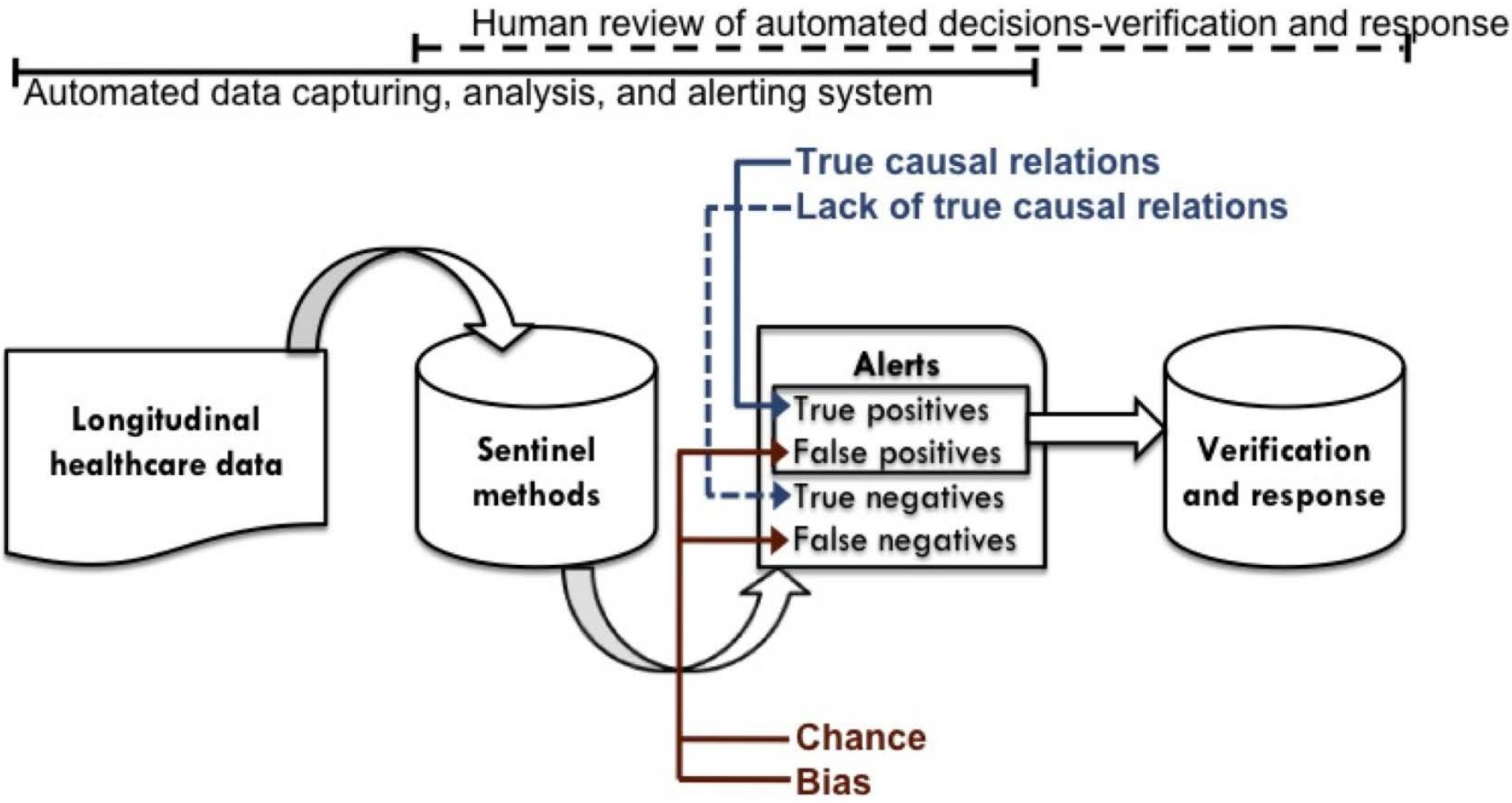
Joshua J Gagne
on behalf of the Taxonomy Work Group

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


Human review of automated decisions-verification and response
Automated data capturing, analysis, and alerting system
True causal relations
Lack of true causal relations
Longitudinal healthcare data
Sentinel methods
Alerts
True positives
False positives
True negatives
False negatives
Verification and response
Chance
Bias

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

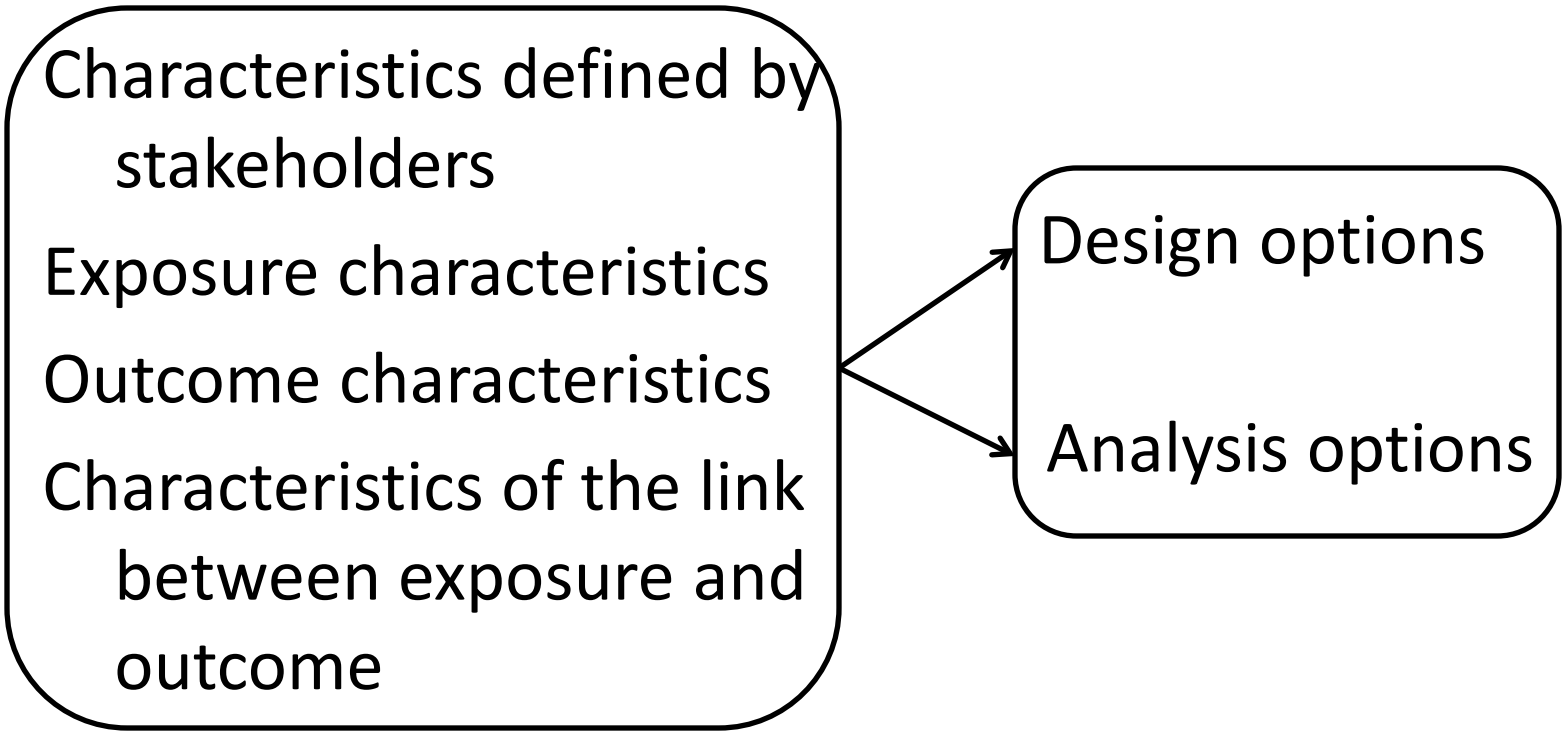
Note: I define "scenario" as a single exposure/outcome pair

- 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

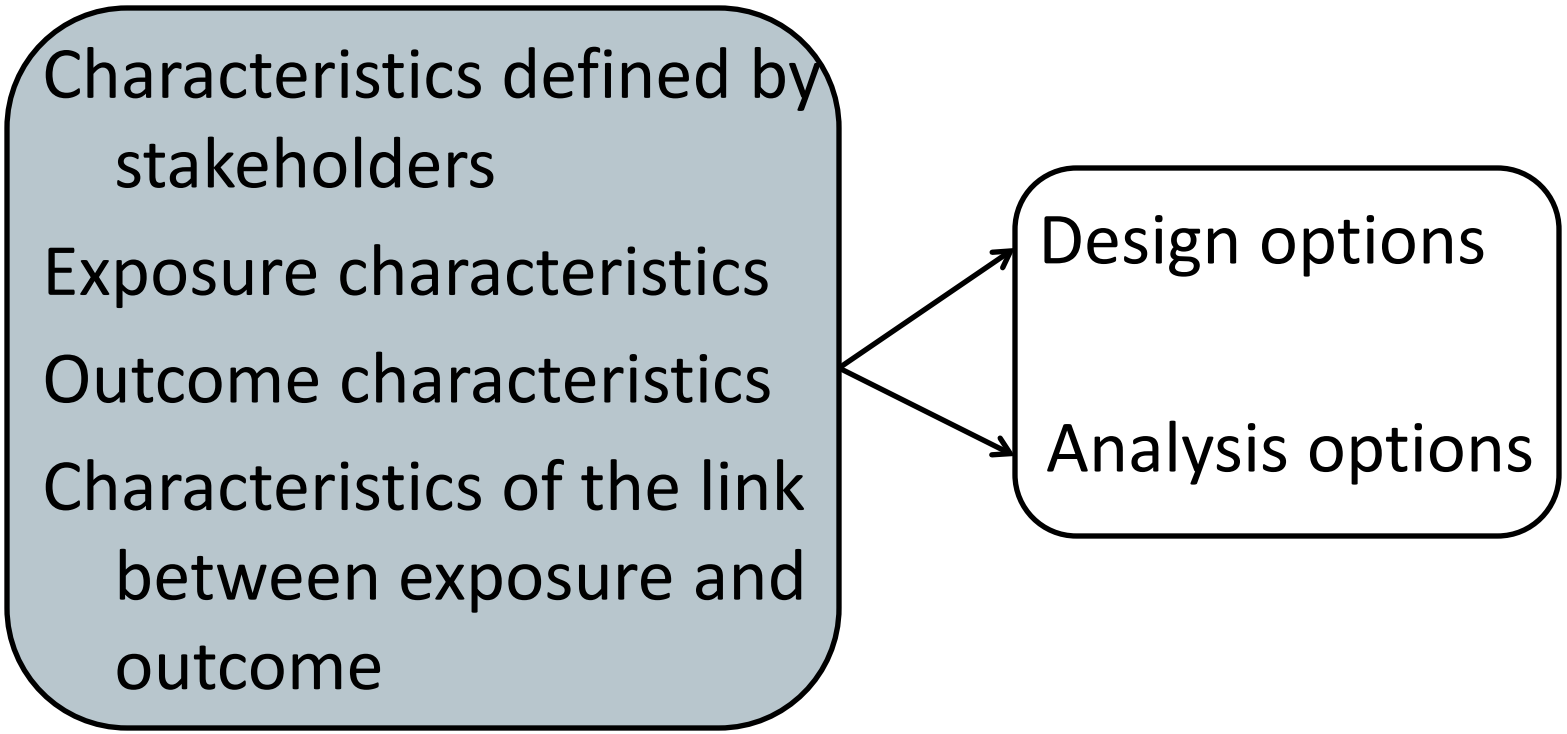
Overall project objectives

- 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



Scenario-method mapping



Scenario characteristics

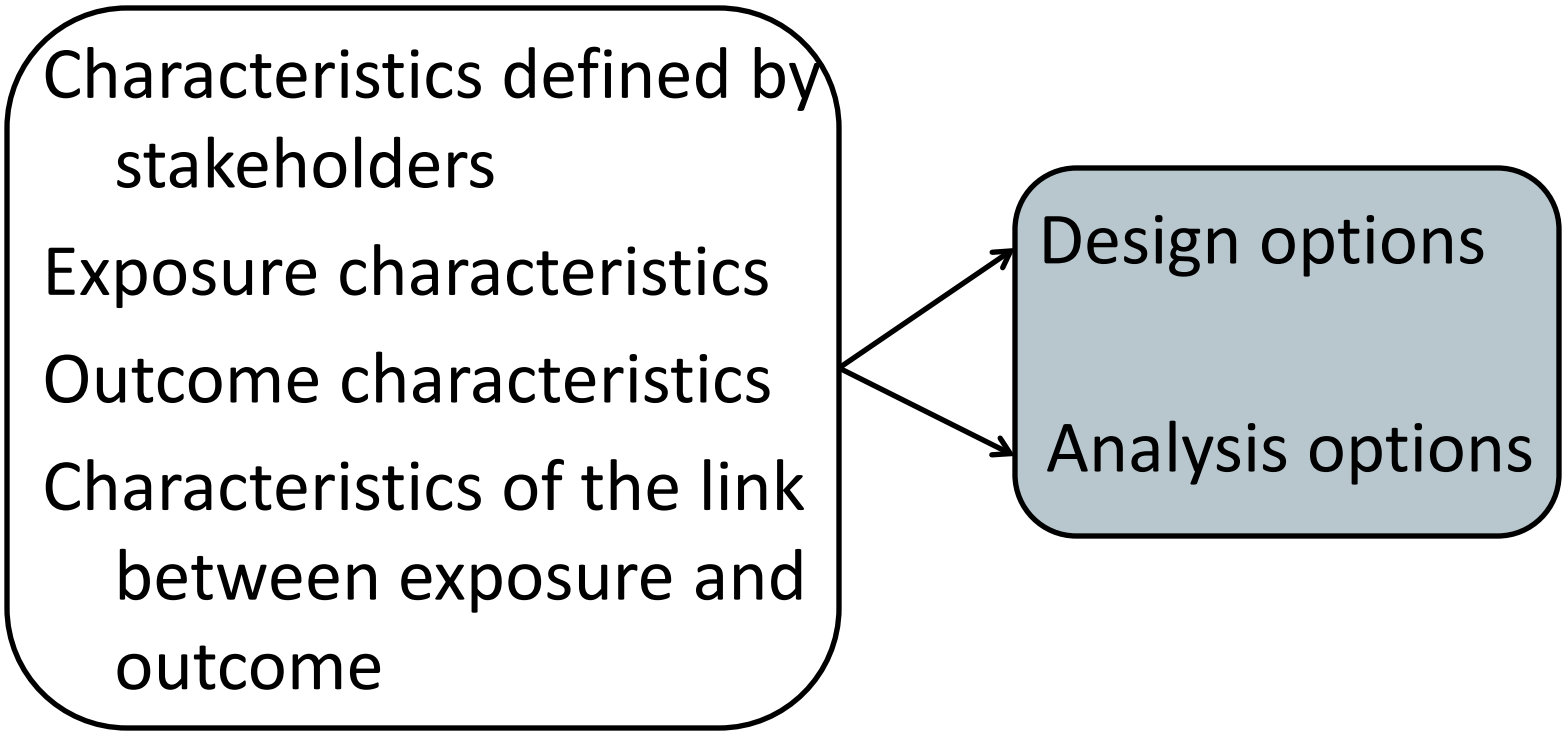
- **Characteristics defined by stakeholders**

Table 2. Scenario characteristics determined by stakeholder/investigator 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

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



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: rosuvastatin and rhabdo

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

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios								
Characteristics determined by stakeholder/investigator			Characteristics inherent to the specific expo					
			Exposure characteristics			Characteristics of the (potential) exposur		
Effect measure of interest	Number of comparison groups	Comparison exposure	Background frequency of use in population	Utilization trend in population	Use pattern	Onset of exposure risk window	Duration of exposure risk window	Strengt confoun: At baseline
Difference measure	One	Active comparator	Infrequent	Changing (increasing, decreasing, cyclical)	Long-term	Immediate	Long	Needs to be addressed
								Negligible
							Short	Needs to be addressed
								Negligible
						Short	Long	Needs to be addressed
								Negligible
							Short	Needs to be addressed
								Negligible
					Short-term	Immediate	Long	Needs to

Example: rosuvastatin and rhabdo

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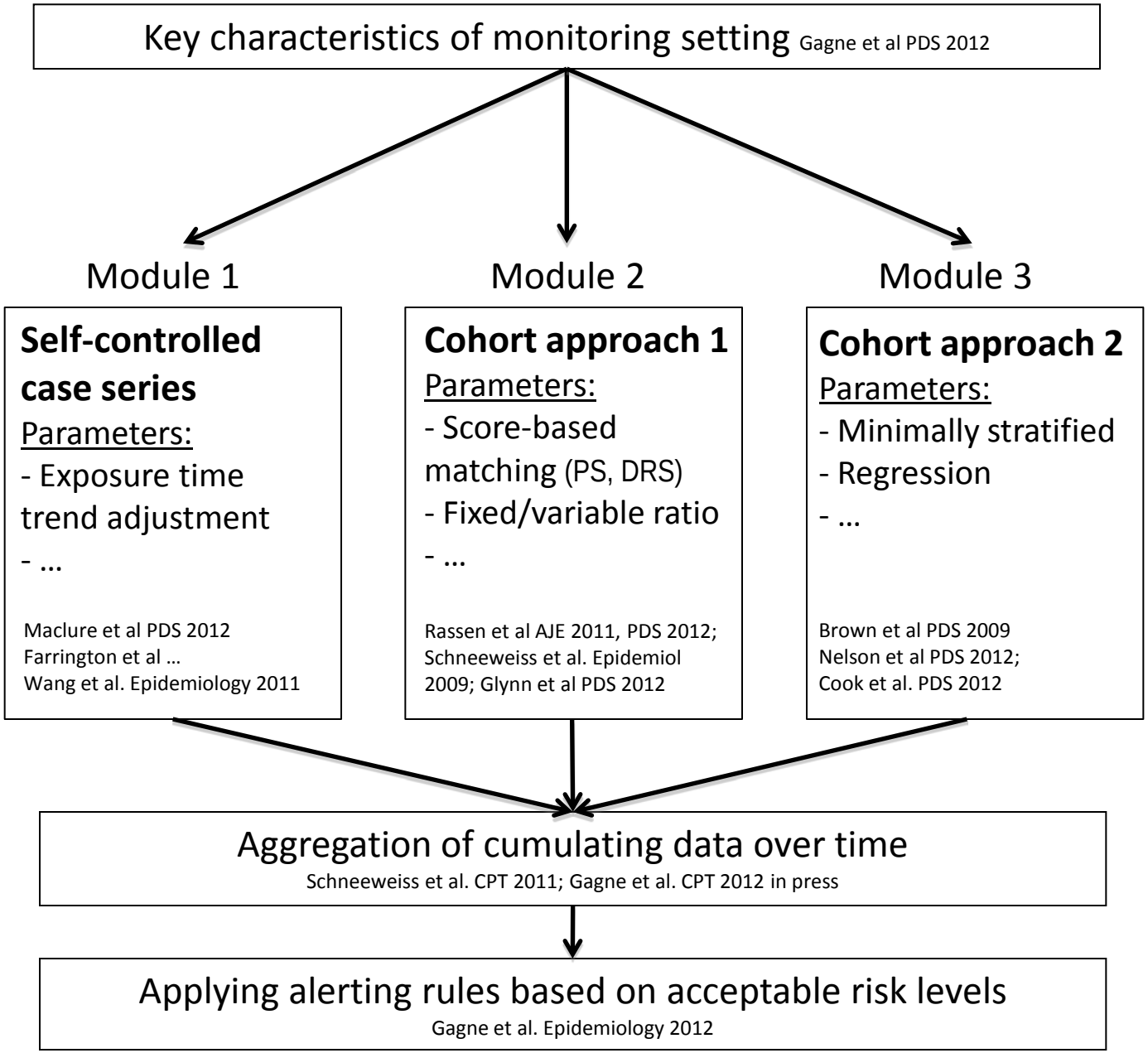
							Short	Needs to be addressed
								Negligible
					Short-term	Immediate	Long	Needs to

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
Module 2
Module 3
Self-controlled case series
Parameters:
- Exposure time trend adjustment
- …
Maclure et al PDS 2012
Farrington et al …
Wang et al. Epidemiology 2011
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
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
(v1.0 11/27/2012)

		Determined by stakeholder/investigator			Exposure			
Exposure	Outcome	Effect measure of interest	Number of comparison groups	Comparison exposure	Background frequency of use in population	Utilization trend in population	Use pattern	
Options:		difference measure	one	active comparator	more frequent	uniform	short-term (including intermittent)	im
		relative measure	multiple	truly unexposed	less frequent	changing (increase, decreasing, cyclical)	long-term	sh
		both						

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