Mini-Sentinel Recommendations for New Safety Surveillance Methods

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Map of methodologic domains

Data capacity	Distributed methods	Alerting strategies

• **Integrity**
– Common data model
– Data completeness
– Data validity
– HOI validation
• **Environments**
– Claims
– EHRs
  • Ambulatory
  • Inpatient
– Registries
– Other (blood banks, genetic data, etc.)
	• **Distribution and retrieval**
	• **Anonymous linkage across sources**
	• **Distributed multivariable analysis**
	– Horizontal
	– Vertical
		• **Design & validity**
		– Expedited design choice
		– Automated confounding adjustment
		• **Performance**
		– Sequential testing
		– Non test-based
		– Decision analytic approaches
		• **Special aspects**
		– Drugs, vaccines, biologics, devices

Applications
• Oral antidiabetic agents and MI, rotavirus vaccine and intussusception, etc.

Issues

- Distributed data handling and analysis
- Accounting for misclassification of exposures, outcomes, covariates
  - For different types of conditions and medical products
- Adjustment for confounding
- Handling unpredictable uptake of new products
- Performance of alerting algorithms to identify "sufficient" excess risk
- Incorporating active surveillance into a decision science framework
  - Estimating benefits/risks of additional surveillance vs regulatory action in the face of an alert

Methods to improve Data Capabilities

- Fast query tools and more sophisticated modular programs
- Health Outcomes of Interest (HOI) evidence reviews/reports
- Linking between data types with/without direct patient identifier ("anonymous linkage").
  - claims to registries, claims to EHRs, claims to claims, etc.
- Late and missing data methods

Improved Methods for Distributed Systems

- Distributed multivariable analysis of horizontally and vertically partitioned data

Methods for improved alerting: Design

- Develop framework to assess when database surveillance can be valid and useful
- Create an operational framework for an active monitoring system, esp. NMEs
  - Focus first on claims, then add additional data types.
  - Emphasize approaches that simplify protocol design and execution.
- Finish mapping of safety questions to designs and analytic choices (incl. methods for developing signal alerts)

Methods for improved alerting: Validity

- Improve validity of refinement methods
  - Account for misclassification (e.g., sampling strategies to validate outcomes in near real-time)
  - Better confounding adjustment, e.g., Propensity Score for >2 exposure categories; dealing with missing covariates in EMR data
  - Develop standard sensitivity analyses
  - Adjust for time-varying confounders
  - Methods for long latency outcomes

Methods for improved alerting: Performance

- Additional sequential testing methods
  - Special methodological issues in a distributed environments
  - Flexible methods for risk/rate difference, risk/rate ratio or hazard ratio effect measures.
- Evaluate non test-based approaches
- Evaluate decision-analytic approaches
- Develop a testing environment that mimics monitoring situations:
  - An evaluation metric that includes timing and preferences
  - Empirical and simulated data

Methods for active surveillance of different product classes and combinations

- Blood and blood products
- Tissue allografts
- Devices
- Biosimilars
- Drug-drug interactions

Methods for rapid follow-up of signals (Signal Evaluation)

- Extend signal cluster detection methods to explore whether signals cluster
  - In time
  - Across subgroups

Methods for detecting unanticipated, non-specific adverse events (Signal Generation)

- Methods for non-specific (i.e., many-by-,many) pairs
  - Large number of drugs against validated HOIs
  - A scaled-up monitoring approach
- Approaches to evaluate signal generation methods
  - All drugs by all codes and code clusters
  - Need to clarify the role of the system's prior probability

Thank you