

Operating Characteristics of Systems for Active Safety Surveillance

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What's Coming

- Pre-specified outcomes
 - Context
 - A “small” number
 - Rich prior experience
 - Sensitivity and specificity
 - Outcome definition
 - Collateral hypotheses
- Non-pre-specified outcomes
 - Context
 - Many, many candidates
 - Vast, potentially relevant medical information
 - Same as above
 - Sensitivity and specificity
 - Outcome definition and extension, through the use of
 - Collateral hypotheses

Pre-Specified Outcomes

Where Pre-Specification Arises

- A prior hypothesis
 - *Causality*. Pharmacology, animal experience, analogy
 - *Relevant Severity*. Expectation of relevance to clinical decision-making
- A check-list of frequent classes of effect across many drug classes
 - Allergy and its manifestations
 - Integument
 - Nervous system
 - Ophthalmologic
 - Hematologic

Where Pre-Specification Ought Not Be

- Manifestations of the disease under study
 - Asthma – sudden death
 - Diabetes – MI
 - Multiple sclerosis – CNS deterioration
 - Rheumatoid arthritis – autoimmune disease
- Indications and contra-indications to the drug/biologic
- Manifestations of the care setting
 - Specialist diagnoses under specialty care
 - Well-child variants such as minor malformations
- *c.f.* caveats for Comparative Effectiveness Research
 - Topics are suitable for research (with care) not surveillance

A Limited Number of Scenarios

- Sensitivity
 - Everything measurable is detectable in the fullness of time, with lots of use
 - Key question is sensitivity-time function
 - The ability signal early is crucial
- Specificity
 - What proportion of noncausal product-outcome associations are flagged as possible “Signals”?
 - Does not need to be high, as the number of flagged cases will be small because of the small number of pre-specified outcomes

Pre-specified Outcomes

- The goal of high sensitivity requires that the *definition* have high predictive value
- Definition includes timing
 - Quick: Angioedema, anaphylaxis, intussusception
 - Weeks: ITP, GBS
 - Months: VTE
 - Years: MI
- Inception cohorts a necessity
 - Difficult enough to track determinants of initiation
 - Determinants of adherence next to impossible in a screening context
 - Only relatively short-term outcomes are accessible to surveillance research

Non-Pre-Specified Outcomes

Where Non-Pre-Specification Arises

- Universal experience of surprises
 - *No prior causal hypothesis. No prior example.*
 - *C.f. almost all the pre-specified hypothesis before examples were first seen*
 - *Sometimes bad enough to cause market withdrawal.*
 - *E.g. valve disorders, sudden death, PML*
- Lack of full knowledge of drug/vaccine/device effect
 - Information outside of targeted receptors or actions may be broad and nonspecific
 - Treatment conditions may differ essentially from test conditions
 - Patients: age, comedication, illness, pregnancy
 - Usage: duration, adherence

A Very Large Number of Scenarios

□ Sensitivity

- Still a desideratum, but now limited by the cost of false-positives
- Early signaling is likely to cause confusion not light
- Needs to be back-calculated from the affordable specificity

□ Specificity

- The major cost of screening is the cost of evaluating false positives
 - Automated next steps help to some extent
 - Personnel-intensive evaluation of hypotheses
- If I have staff enough for 25 intensive medical evaluations each year, and there are 50 new products and 500 possible screening outcomes each, then roughly I can only lower the specificity to 99%.

Evolving Definitions

- Data are taken at the level of precision provided by the coding scheme
- The cost of poor specificity means that there need to be quick evaluations available in the data
- Orthogonal hypotheses
 - Interpretations of observed effects
 - Leading to predictions about other effects that are
 - Not logically implied by the first observations
 - Immediately observable (testable!) in the data
 - E.g. *forme fruste*, other consequences of same hypothesized pathology, alternative coding of the same phenomenon

What are the Needed Operating Characteristics?

The Menu is Not *Prix Fixe*

- Pre-specified outcomes
 - Care in definition of outcome and timing required
 - High sensitivity and modest specificity are the statistical goals
- ➔ **Place reliance on formalized inference.**
- Non-pre-specified outcomes
 - High specificity is the first order of business
 - Flexible and quick re-examination of data-driven hypotheses is mandatory
- ➔ **The machine invokes and supports the human pattern-recognizer and hypothesizer early in the surveillance cycle.**



Thank You!