

**OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP**

**Opportunities for Signal Detection
in an Active Surveillance System**

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Routine quantitative signal detection

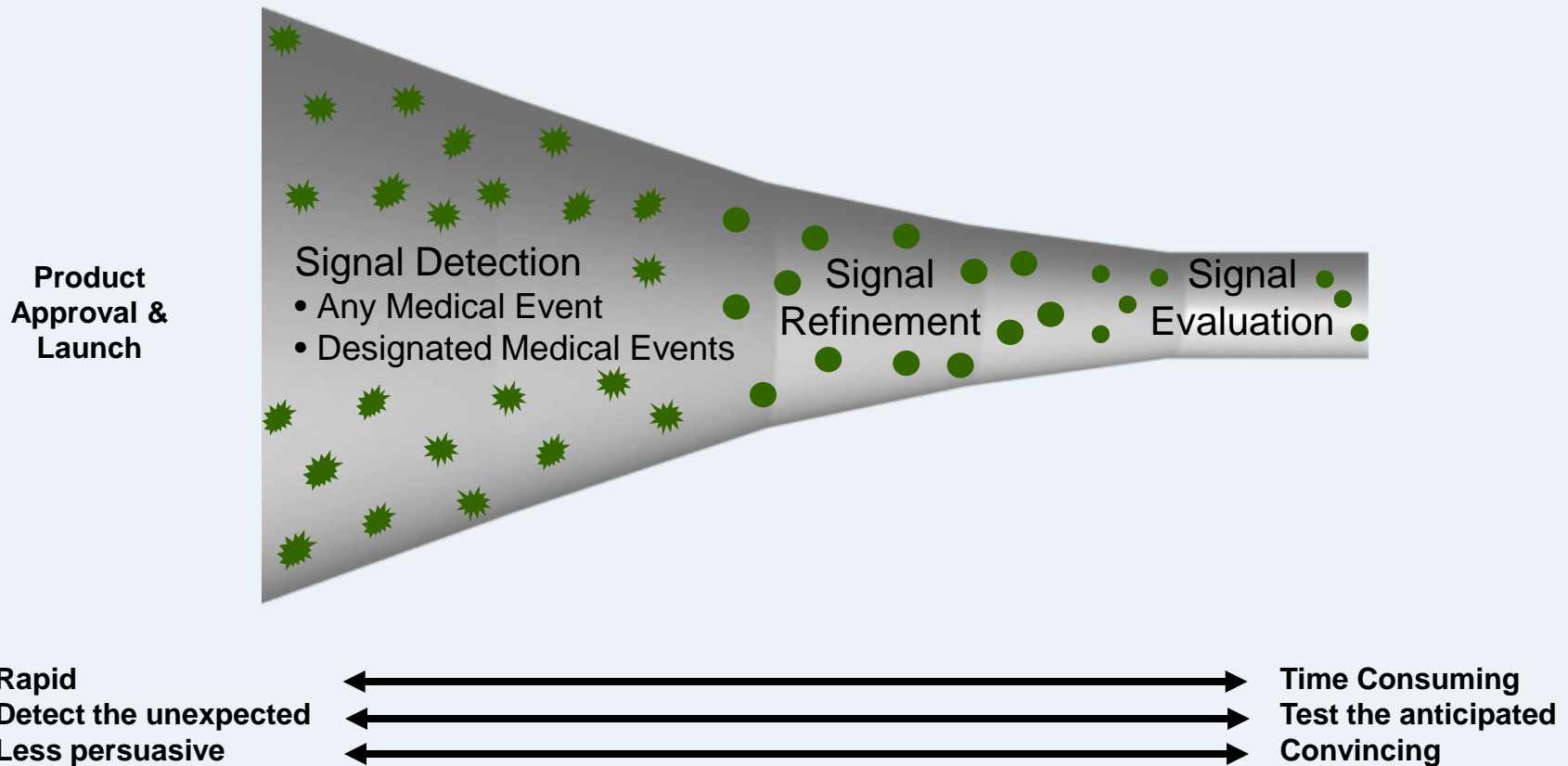
- Done primarily, though not exclusively, on SRS data
- Detect potential signals for further investigation that not readily recognisable on a single case report nor otherwise readily apparent at case entry
- Enhance rather than replace other methods of signal detection
 - Qualitative filters
 - Triage of statistical outputs
- Help to detect signals earlier, more effectively

Signal of suspected causality - definition

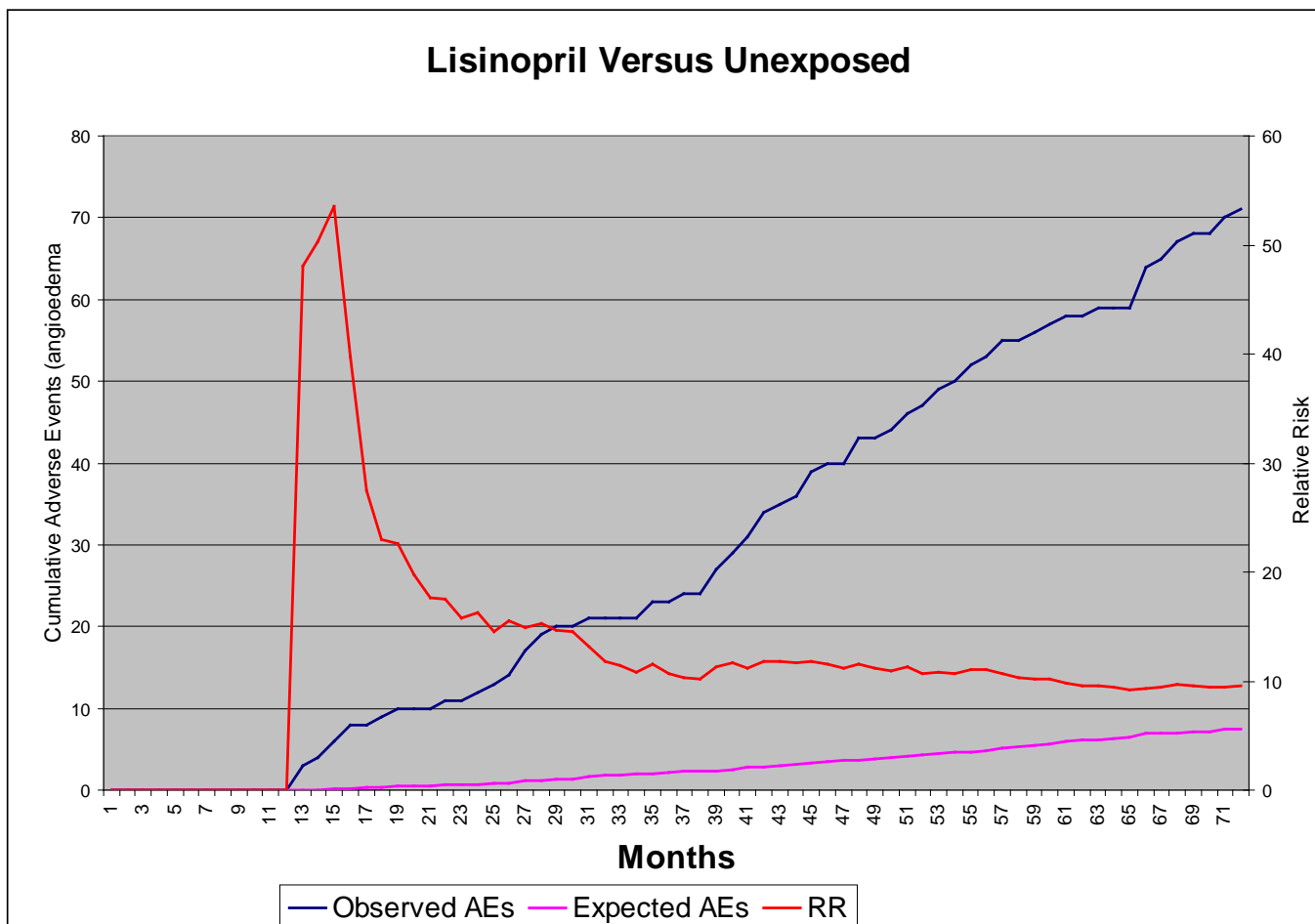
“Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifactory action.”

Ref CIOMS VIII Practical Aspects of Signal Detection
in Pharmacovigilance 2009

Novel Use of Claims & EMRs for signal detection/refinement



Recording of angioedema for lisinopril users compared to non-users: 2000-2005

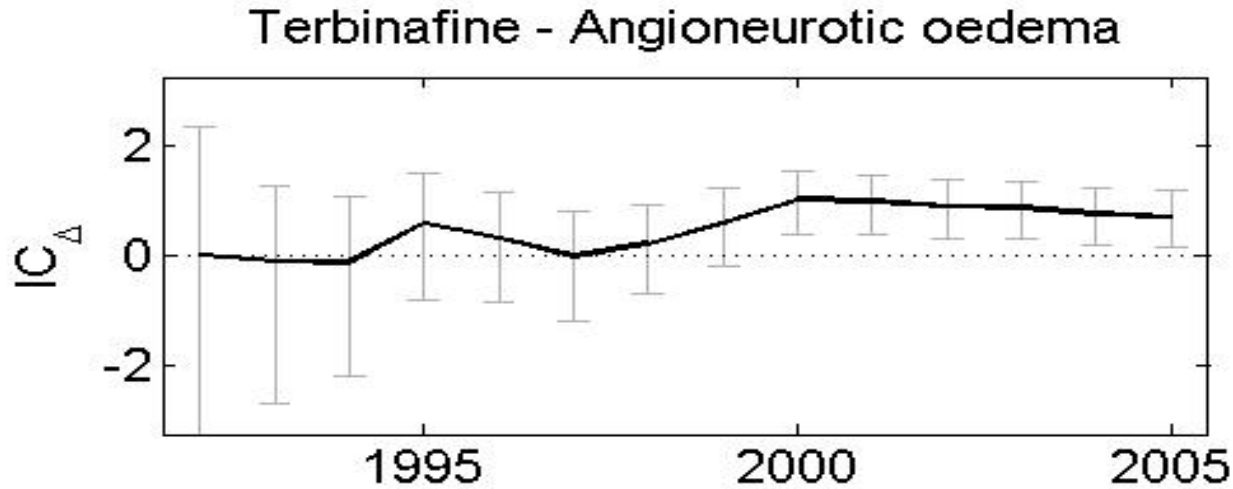


Unpublished data based on work in Brown *et al.*, (2007, 2009) in PDS).
Contact:
jeff_brown@hphc.org

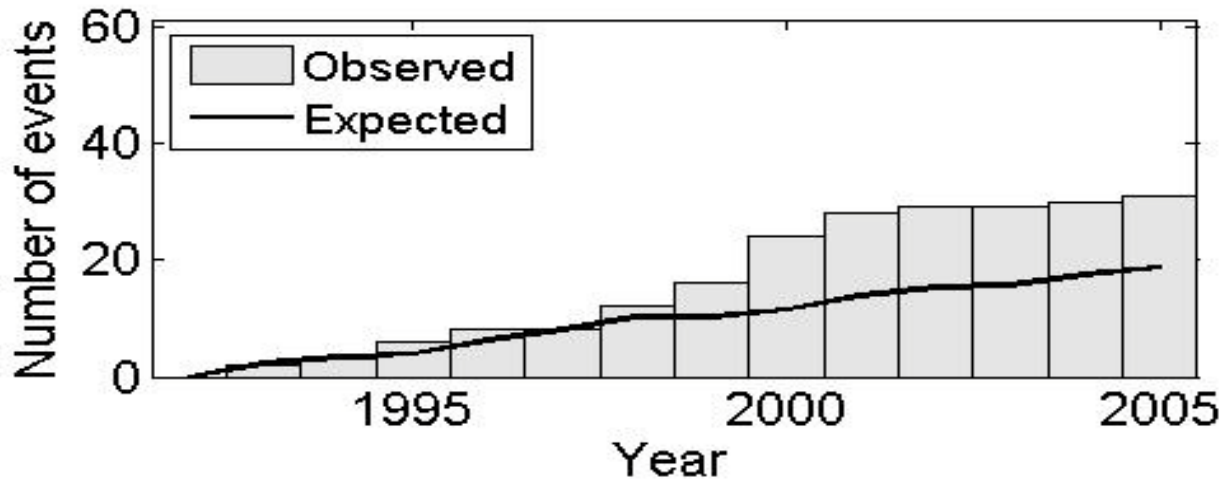
Signal at month 13; 3 observed and 0.06 expected

Note: Base-case analysis. Outcome: Angioedema. Adjusted for age, sex, and health plan.

Retrospective identification example of labeled AE using EMR screening



Ref Noren et al 2010 DMKD



Challenge of signal detection capability in observational databases

- Consider a database covering 20 million patients
- 1:200 of population get the specific drug within a year
 - 100,000 patients
- Of these 1:2000 get a specific AE
 - 50 events
- Quite a large number of events...

Challenge of signal detection capability in observational databases

- All events may not be captured
- Event not accurately/consistently coded
 - Hard to cluster all related events together
- Missing key clinical information because of lack of clinical suspicion
- Then consider a prevalent non-drug disease...

Challenge of signal detection capability in observational databases

- Even in large observational databases may not have sufficient power
 - Risk missing signals
- Loss to follow up, biases in recording, and other general challenges with observational data
 - Analysis across multiple databases will help with power, but not biases
 - False positive and negative signals

Advantages and challenges with patient records and claims data

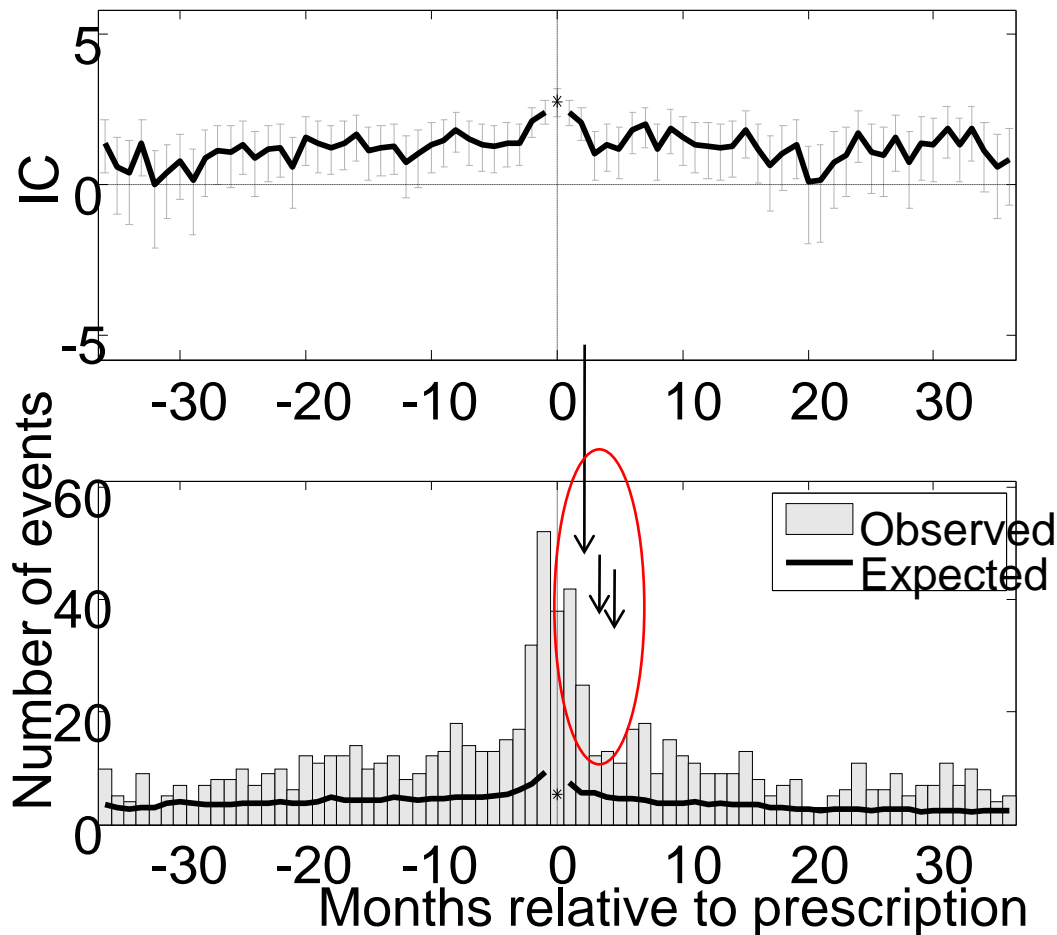
- Rich data
 - Time stamped diagnoses (without any requirement of clinical suspicion)
 - Recorded exposure; and reliable non-exposure
 - Detailed information on disease history prior to drug exposure
 - Other data: test results, hospital referrals and admissions, surgical procedures, notes, symptoms, signs and administrative data
 - Often linked/can be linked to other rich healthcare data
- No suspected link between prescription and outcome makes screening challenging

Heterogenous types of safety signal in EMR and Claims data

- New Adverse drug reactions
- New info on known ADRs
 - Unexpected time to onset pattern
- Stratum specific/ Effect modification effects
 - Age, sex, dose
- Underlying Disease
- Periodic patterns
- Drug-drug interactions

From Norén et al 2010

Acute pancreatitis recording relative to omeprazole prescription in an EMR



As presented
in Noren
et al 2008

Examples of emerging research on signal detection in observational databases

- Norén, GN Bate A et al (2008). Temporal pattern discovery for trends and transient effects: its application to patient records. ACM KDD proceedings, Las Vegas, ACM.
- Jin HW, Chen J. (2008). Mining unexpected temporal associations: applications in detecting adverse drug reactions. IEEE Trans Inf Technol Biomed 12(4): 488-500.
- Norén, GN, Hopstadius J et al. (2010). Temporal pattern discovery in longitudinal electronic patient records. Data Mining and Knowledge Discovery 20(3): 361-387.
- Walker AM (2010). Signal detection for vaccine side effects that have not been specified in advance. Pharmacoepidemiology and Drug Safety 19(3): 311-317
- Schuemie, M. Methods for drug safety signal detection in longitudinal observational databases: LGPS and LEOPARD." Pharmacoepidemiology and Drug Safety. In Press

Questions about signal detection in observational databases

- How well can signal detection work on observational data?
- Need to know performance characteristics?
- What is success in signal detection?
- Not implicit that success is the same as for signal evaluation
 - Accuracy is a primary goal for signal evaluation of a specific issue – in detection would one be prepared to sacrifice accuracy for specific issues for an overall decrease in number of false positive and false negative findings?
- Not necessarily the case that best methods for SE will be best for SD in EMRs
 - Nor necessarily same methods as for signal detection in spontaneous reports
- We need empirical results to support or refute opinions/perspectives/speculations on the potential value of signal detection in observational data

Conclusions

- Quantitative approaches add value to signal detection on spontaneous reports – might they do the same on observational data?
- Some emerging evidence that analysis of longitudinal observational data (EMRs and Claims databases) can contribute to process of signal detection, but limited
 - Huge challenge remains of how to separate potential true findings from vast number of false positives that could emerge
 - Such data may allow the detection of novel types of safety signals
- Pharmacoepidemiological studies for hypothesis evaluation will continue to have a crucial, routine role in drug safety
 - We need to ensure that they can be done as effectively as now
 - Concerns over signal detection and evaluation in the same data set need to be examined
- We need more data on signal detection performance on observational data - hope OMOP results can provide this