# Safety surveillance of spontaneous reports to observational databases: current status and future horizons

Andrew Bate
Senior Director, Analytics Team Lead, Epidemiology
ICPE, Signal detection training coursen
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# Disclosures

- I am a full time employee of Pfizer and hold stocks and stock options

# Overview

- Spontaneous reports - current status and future work
  - Focus on quantitative analysis of reports alone
- Real world data for analysis
  - Examples of observational databases
- Recent and ongoing global initiatives on safety surveillance research
- Differing data access models for surveillance
  - Concept of Centralized v distributed/federated sets of multiple database

# Spontaneous report screening- a decade or so ago

- Quantitative metrics for screening spontaneous reports
  - IC, EBGM, PRR, ROR - Doubts as to their effectiveness, and if and how to best implement
- Inconsistent use and occasional misuse
  - hypothesis generation v testing
- Critical role of clinical review not always appreciated
- Limited quantitative signal detection on other data sets
- Vast majority of signal detection in post-marketing relied on spontaneous reports

# Metrics used in quantitative screening of spontaneous reports

2 by 2 contingency table

| | AE of interest (y) | Other AEs |
|---|---|---|
| Drug of interest (x) | a | b |
| Other drugs | c | d |

Proportional Reporting Ratio (PRR) =

$$[a \div (a+b)] \;/\; [c/(c+d)]$$

Reporting Odds Ratio (ROR) =

$$[a \div b] \;/\; [c/(d)]$$

Observed to expected ratio [1] =

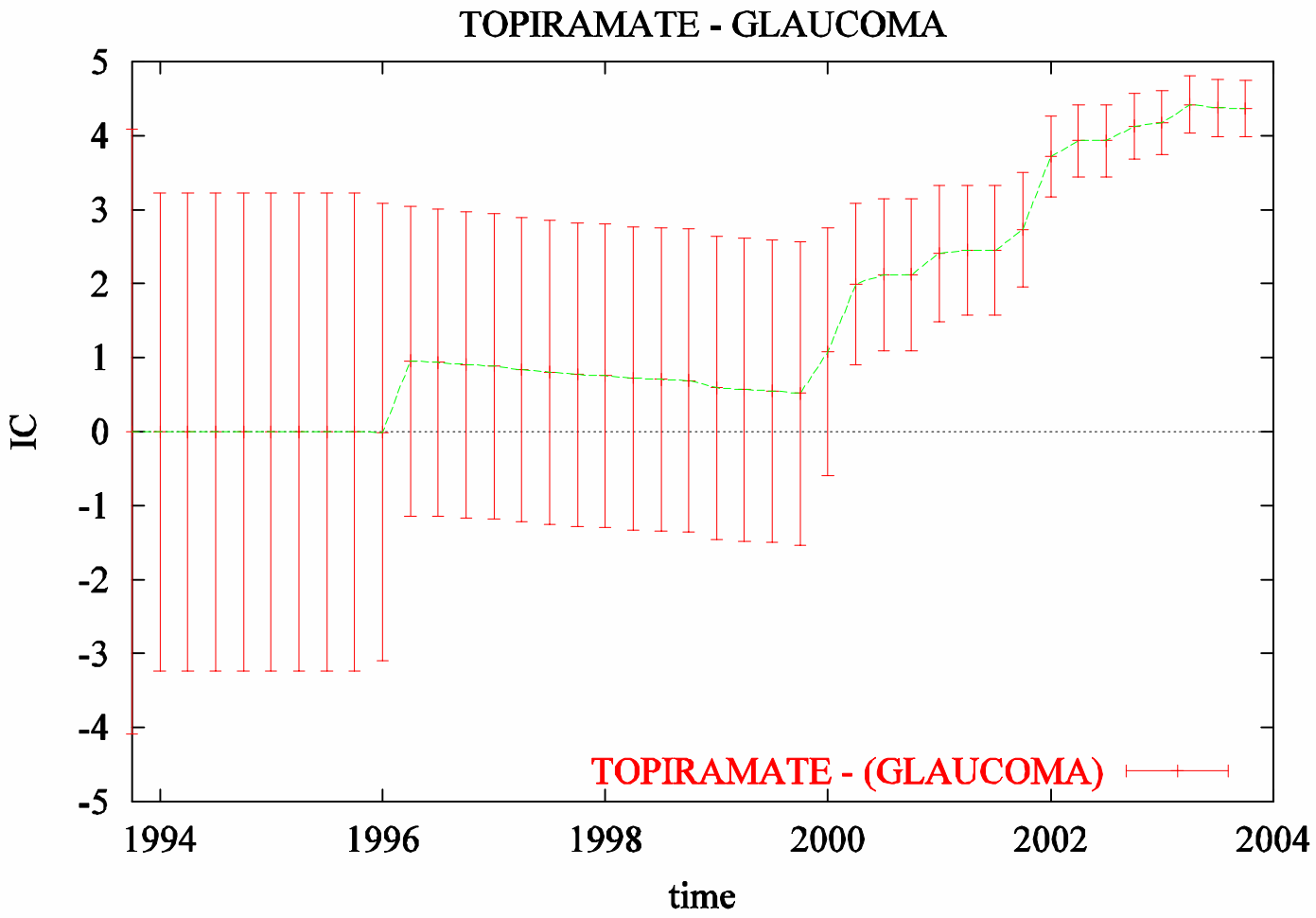
$$[a/(a+b] \;/\; [a+c/\; a+b+c+d]$$

[1] Frequentist basis of EBGM and IC



See Bate and Evans 2009 PDS, for an overview

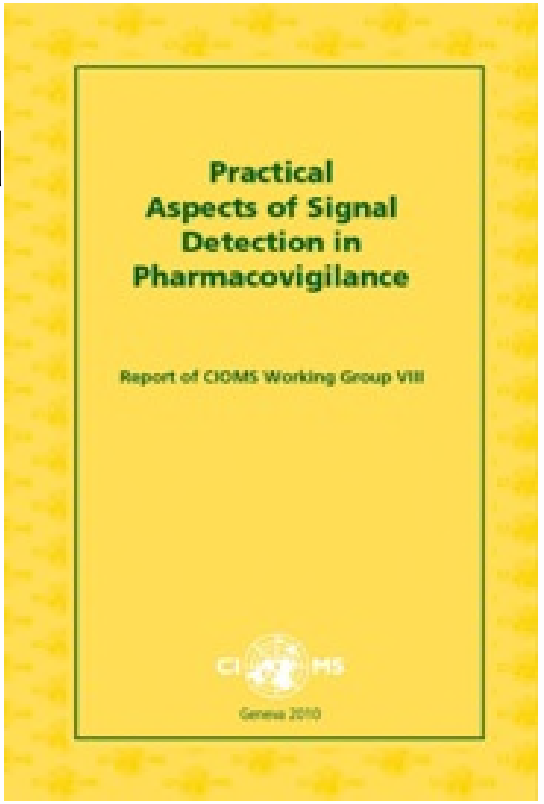
# Change over time for signal detected prospectively using data mining of SRS data




Ref Bate & Edwards 2006 BCPT

# CIOMS VIII and signal detection

- The Council for International Organizations of Medical Sciences (CIOMS) international, non-governmental, non-profit organization established in 1949
- *http://www.cioms.ch/*
- Provide useful points for consideration for all wishing to establish or understand the output of a systematic and holistic strategy to better manage the entire "lifecycle" of a drug safety signal



# The rationale for CIOMS VIII - a personal view

- All stakeholders looking for further clarity on best practices in (quantitative) signal detection
  - Applicable to their organization
- What is the best quantitative method?
- Ought quantitative methods always be used for signal detection?
- How to interpret signal metric scores?
- What are the necessary and recommended steps in a signal detection process?
- Increased international harmonization in signal detection
- Views on where post-marketing safety field is heading

# CIOMS VIII contents

- What it does not do
  - State that any given data mining algorithm is always best
  - Not address in detail signal detection in
    - RCTs
      - Covered elsewhere: CIOMS VI
    - Observational databases
      - Although some thoughts (Emerging and rapidly evolving field)
- What it does
  - Emphasize that  clinical review of data mining algorithm output is critical
  - Make clear that data mining need not be done on every drug safety data set
  - Propose a new definition of signal detection

# 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 verificatory action."

Ref CIOMS VIII Practical Aspects of Signal Detection in Pharmacovigilance 2009

# Spontaneous report quantitative signal detection– status

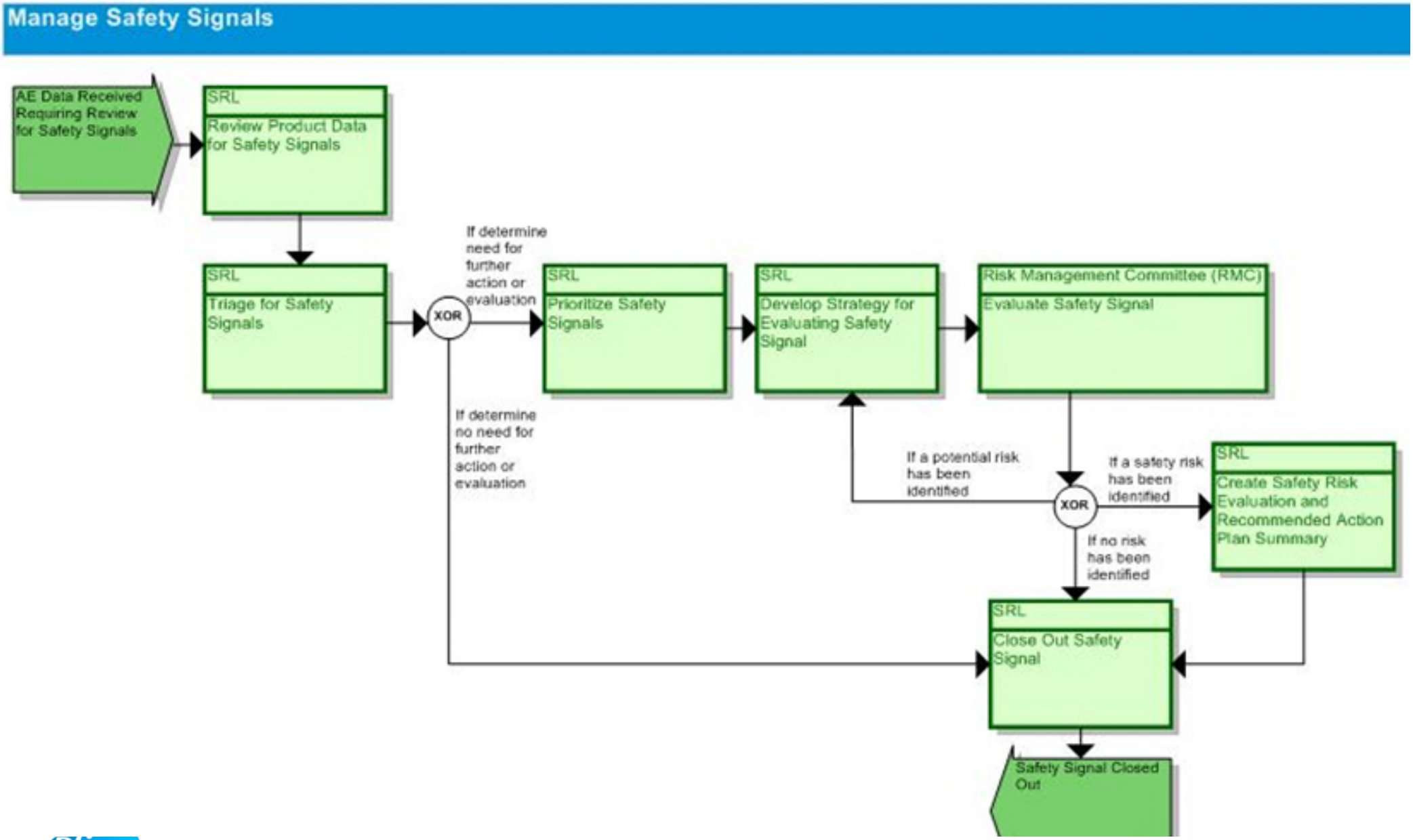
| | |
|---|---|
| • Disproportionality -a useful tool | Yes |
| • Clarity on use of disproportionality | Yes |
| • Clarity on output interpretation | Almost there |
| • Method performance? | Nearly there |
| • Stratification | Nearly there |
| • Place of tools in overall process | Nealy there |
| • Communication | Progress |
| • Recommendations | Some |

Primarily focussed on single drug - single AE detection

# Spontaneous report quantitative signal detection– status

| | |
|---|---|
| • Signal management and embedded in tools | Yes |
| • Quantitative analysis other variables | Some |
| • Drug-drug interaction detection | Some |
| • Leverage of free text data | Some |
| • Methods to improve data quality | Some |
| • More complex clustering | Limited |
| • More complex reasoning/algorithms | Little |
| • Research agenda completed | No |

# Example of a systematic process for Signal management



# Ongoing Misunderstanding

- ”The ’PRR’ of 6 indicates that for this drug the risk of reporting this event is six times higher compared with reference drugs.”
- Should be:

  ”The ’PRR’ of 6 indicates that for this drug the probability of reporting this particular event rather than any other event is six times higher compared to the probability for reference drugs

# Spontaneous report screening- Lessons learnt for application to other data sets

- The challenge of false positives and false negatives and processes to address
  - Bradford Hill criteria
- Imperfect performance and difficulties with assessing performance
- Critical role of terminological challenges
- Performance assessment challenges
- Need for careful communication
- The importance of harmonized definitions

# EMRs and claims data as compared to spontaneous reports for surveillance

- 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
  - Much data in structured fields but different databases may use different terminologies
  - Often linked/can be linked to other healthcare data
  - But challenging for screening that no clinical suspicion link between prescription and outcome

# Some selected observational databases

| Database | Country | Characteristic | Population Size |
|---|---|---|---|
| THIN | UK | GP primary care database | 10.5 M[1] |
| Danish National Health Service Register Database | Denmark | Healthcare registry of care | 5.5 M[2] |
| Premier | US | Clinical data from the hospitals | 130 M+ patient discharges[3] |
| Normative Health Information (NHI) Database | US | Transactional claims records of a commercial health insurer | 60 M+[4] |
| Health Insurance Review and Assessment Service (HIRA) | Korea | Insurance Claims from near universal national system | 48 M[5] |

[1] Blak et al Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Informatics in Primary Care 2011;19:251–5

[2] Furu K. et. al. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. Basic & Clinical Pharmacology &Toxicology 2009; 106: 86-94

[3] Fisher BT et al. In-hospital databases In Pharmacoepidemiology 5th Edn 2011 pp 244-258

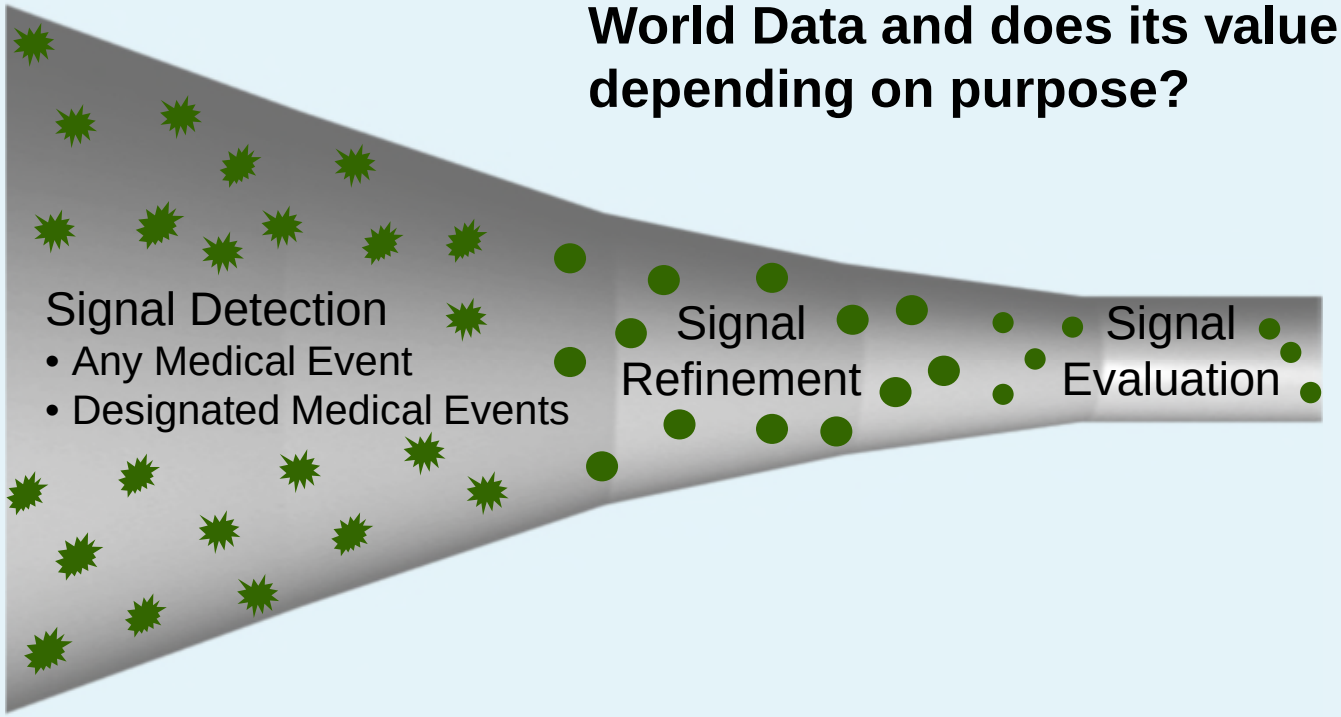
[4] Seeger J, Daniel GW. Commercial Insurance Databases. In Pharmacoepidemiology 5th Edn 2011 pp 189-208

[5] Kimura T et al. Pharmacovigilance systems and databases in Korea, Japan and Taiwan. Pharmacoepidemiology and Drug Safety. 2011; 20: 1237–1245

# Novel Use of Claims & EMRs for signal detection/refinement

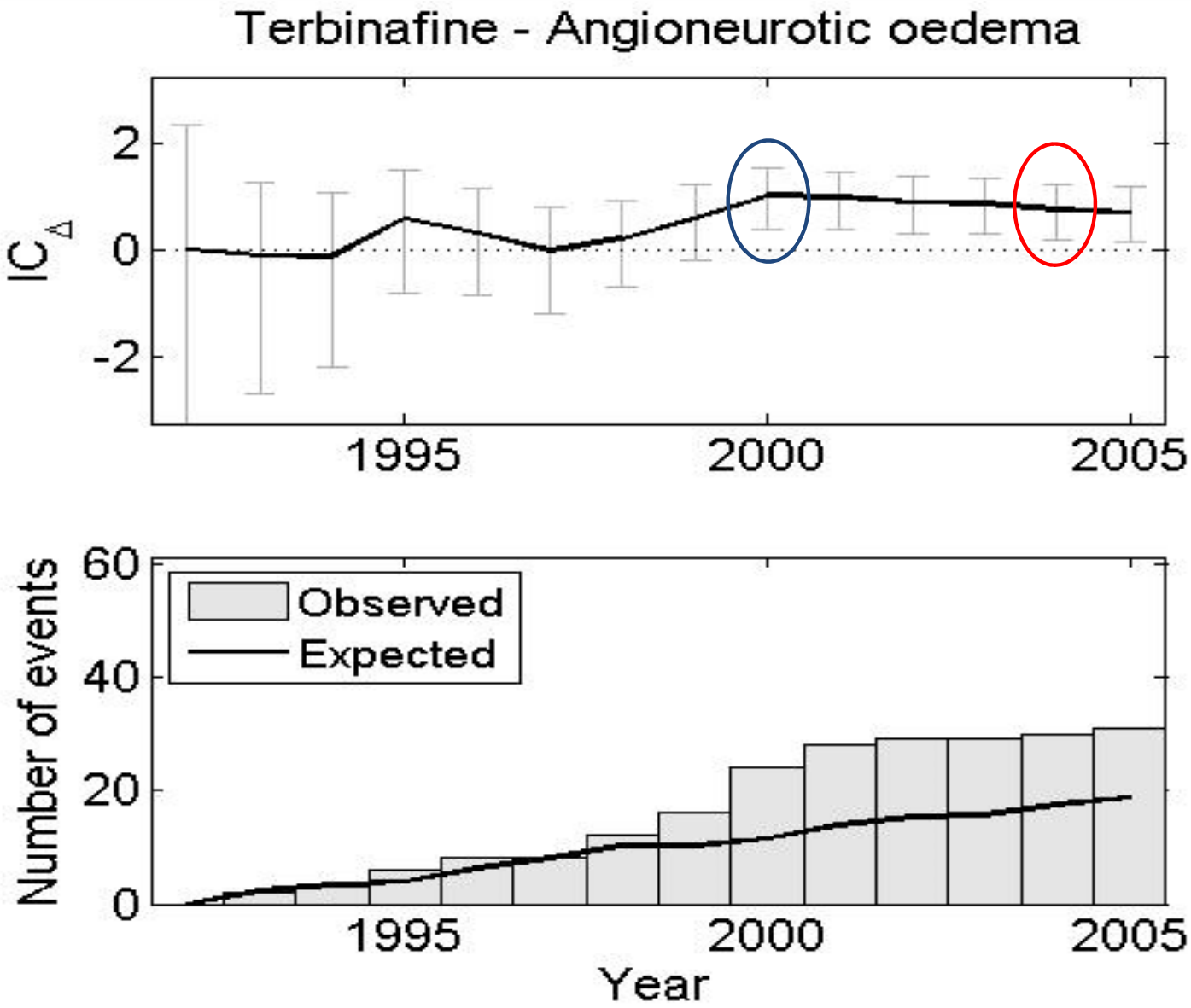
**How to best utilise the wealth of Real World Data and does its value change depending on purpose?**

**Product Approval & Launch**




| | | |
|---|---|---|
| **Rapid** | ⟷ | **Time Consuming** |
| **Detect the unexpected** | ⟷ | **Test the anticipated** |
| **Less persuasive** | ⟷ | **Convincing** |

# Example: Demonstrated Use of EMR Data for Early Identification of AEs



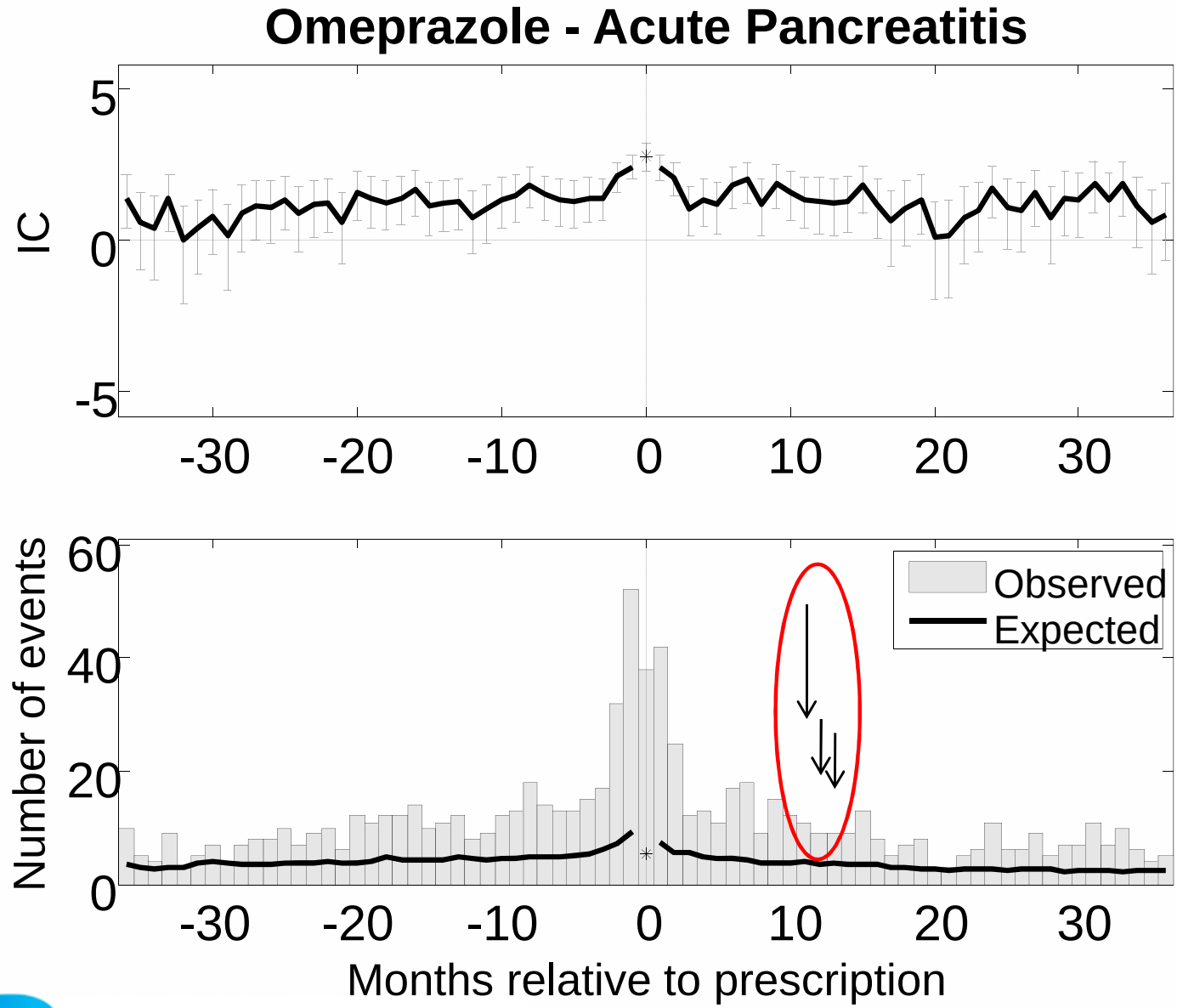

IC$_\Delta$* shows unexpected frequent recording of outcome after terbinafine prescription

Angioedema was labelled In January 2004

* IC$_\Delta$ is the difference in IC before and after prescription on a logarithmic scale

# Novel Insights from Longitudinal Patient Records

## UK EMR (THIN): 3.7 M patients




Information Component (IC)* shows unexpected recording of outcomes relative to time of prescription

Spontaneous reports valuable, but give limited insights in such situations

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* IC is a Bayesian shrinkage observed-to-expected ratio on a logarithmic scale

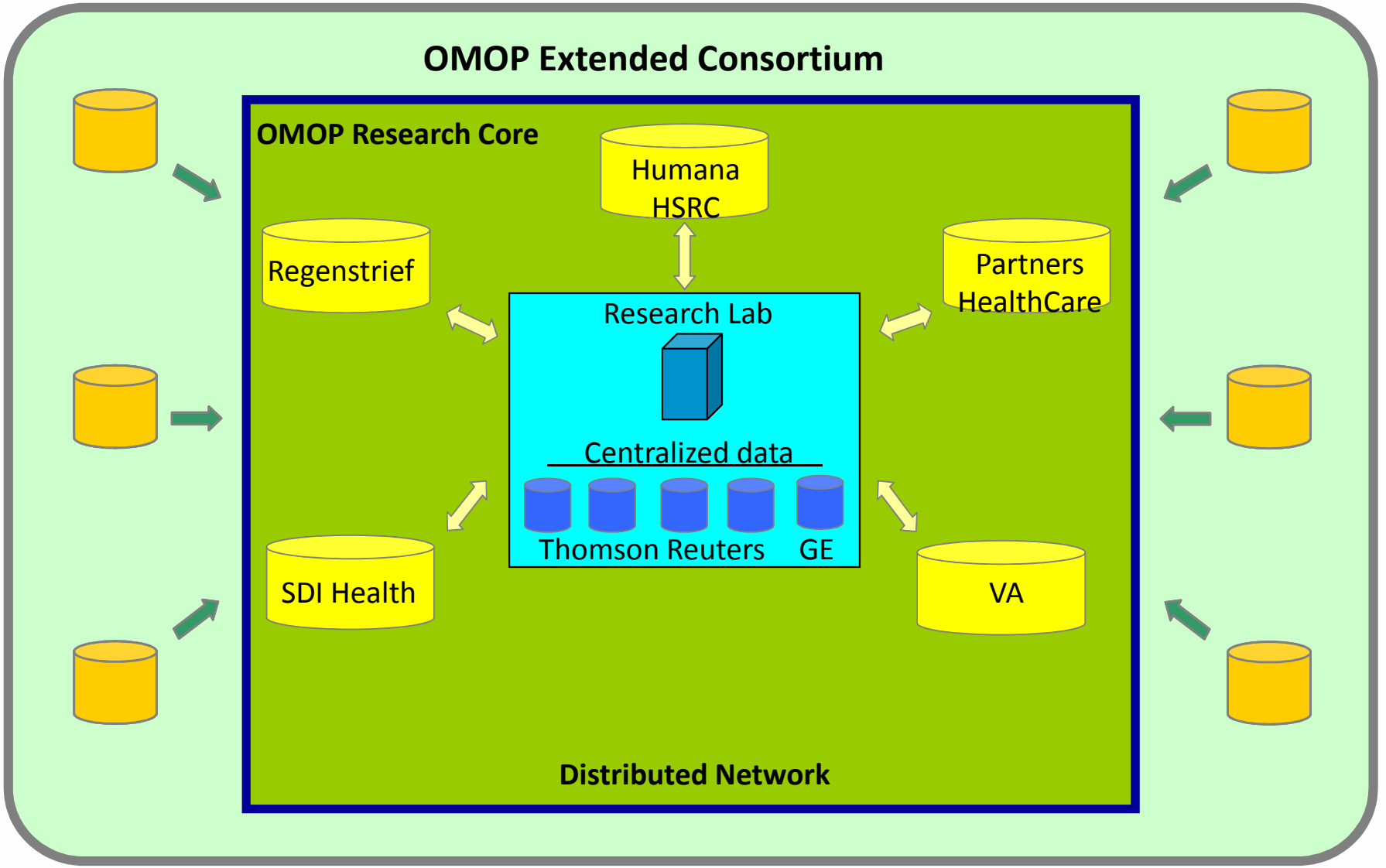
# International and National Initiatives addressing database surveillance

- CIOMS VIII “Practical Aspects of Signal Detection in Pharmacovigilance”
- Innovative Medicines Initiative (IMI) project: PROTECT
  - European Community's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative
- Innovation in Medical Development and Surveillance (IMEDS)
- FDA Sentinel Initiative
- European Commission Seventh Framework Programme (FP-7) of the Research Directorate: EU_ADR
- The Asian Pharmacoepidemiology Network (AsPEN)
- Many other international, national and regional initiatives

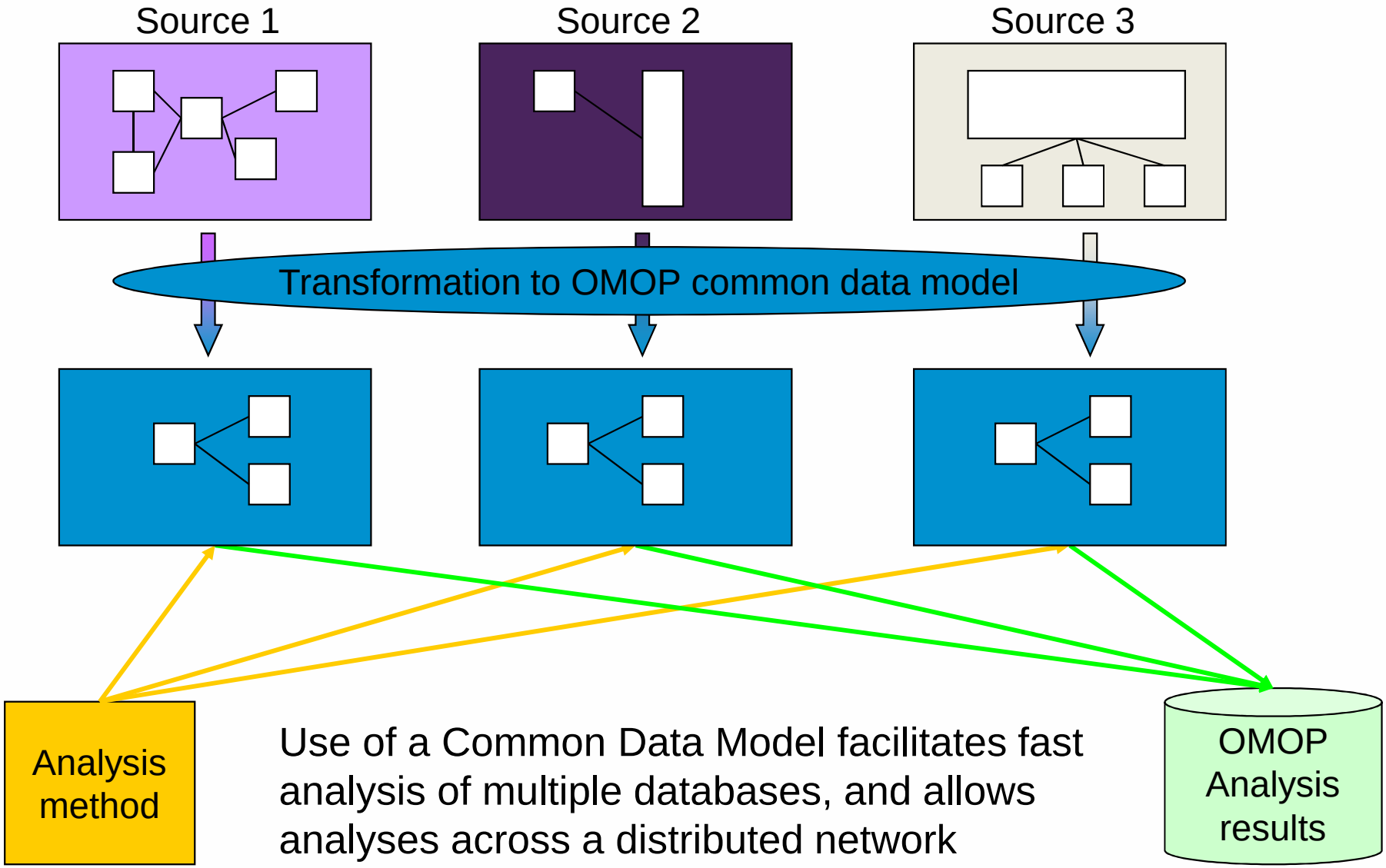
# Innovation in Medical Development and Surveillance (IMEDS)

- IMEDS is a program within the Reagan-Udall Foundation for the US FDA and is a public private partnership created to build upon the significance progress made of research methodology by FDA's Sentinel Initiative and the Observational Medicines Outcomes Partnership (OMOP)
- Primary objective is to advance the science and tolls necessary to support post-market evidence generation on regulated products, including safety surveillance and evaluations, to facilitate utilization of a robust electronic healthcare data platform for generating better evidence on regulated products in the post-market settings
- See: imeds.reaganudall.org

# OMOP Data Community



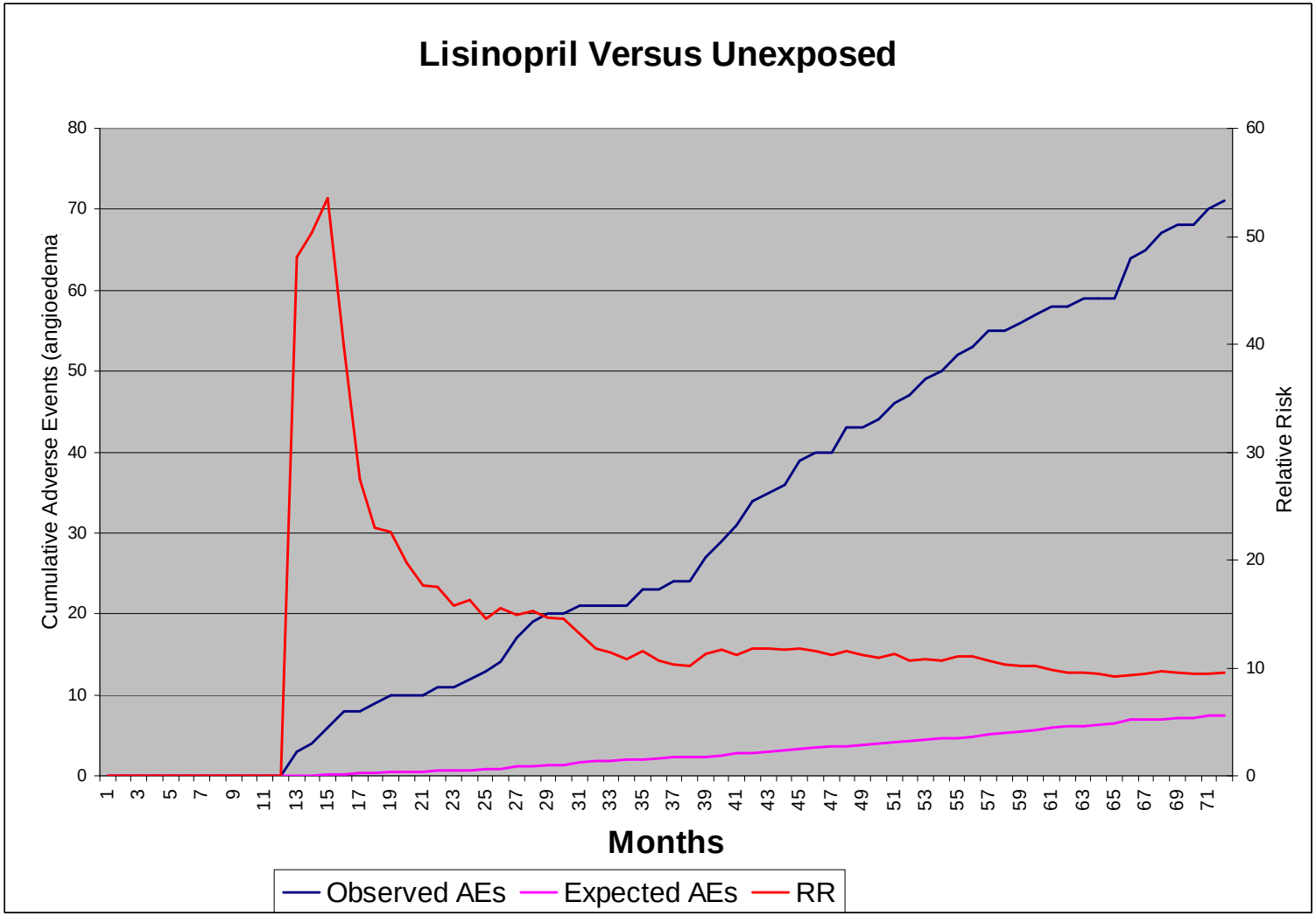
# Common data model role in OMOP Analysis




Use of a Common Data Model facilitates fast analysis of multiple databases, and allows analyses across a distributed network

Reference: OMOP

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




Data from US Health Maintenance Organization research network

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

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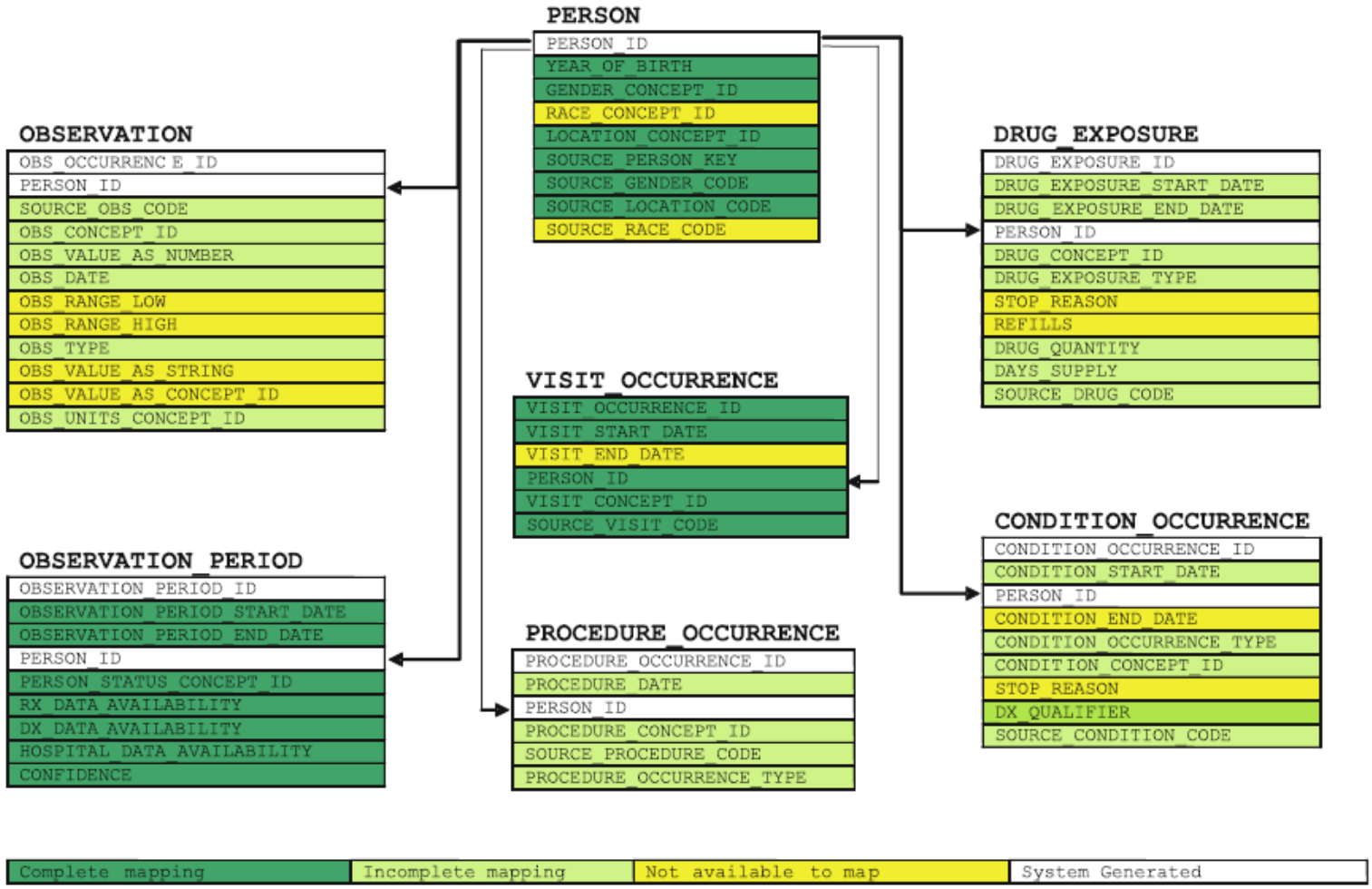
Note: Base-case analysis. Outcome: Angioedema. Adjusted for age, sex, and health plan.

# Database model heat map

Ref Zhou et al 2013

Database model is that of OMOP CDM

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Shows how well different variables convert into a Common Data Model

# Different disciplines with potential methods for safety surveillance

- Traditional epidemiological methods primarily used in formal testing in observational data
  - To some extent have been previously adapted to screening for signals (eg Case Control Surveillance)
- Methods used for drug safety screening of spontaneous reports
  - Implement as near ‘as is’ as possible
  - Adapt and chance as needed for use on longitudinal data
- Methods for screening in RCT research (e. g. meta analysis and/or monitoring approaches) e.g SPRT
- Data mining methods rarely used in drug safety
  - With more extensive use in other large scale screening applications (credit card fraud detection, market basket analysis) etc
- Other ways of classifying methods (eg cross-sectional v temporal focus), what variable values method based on)
- Multiple implementation challenges e.g. best approaches to address confounding in a surveillance framework
  - No implicitly best approach

# Challenging Issues specific to surveillance of observational databases

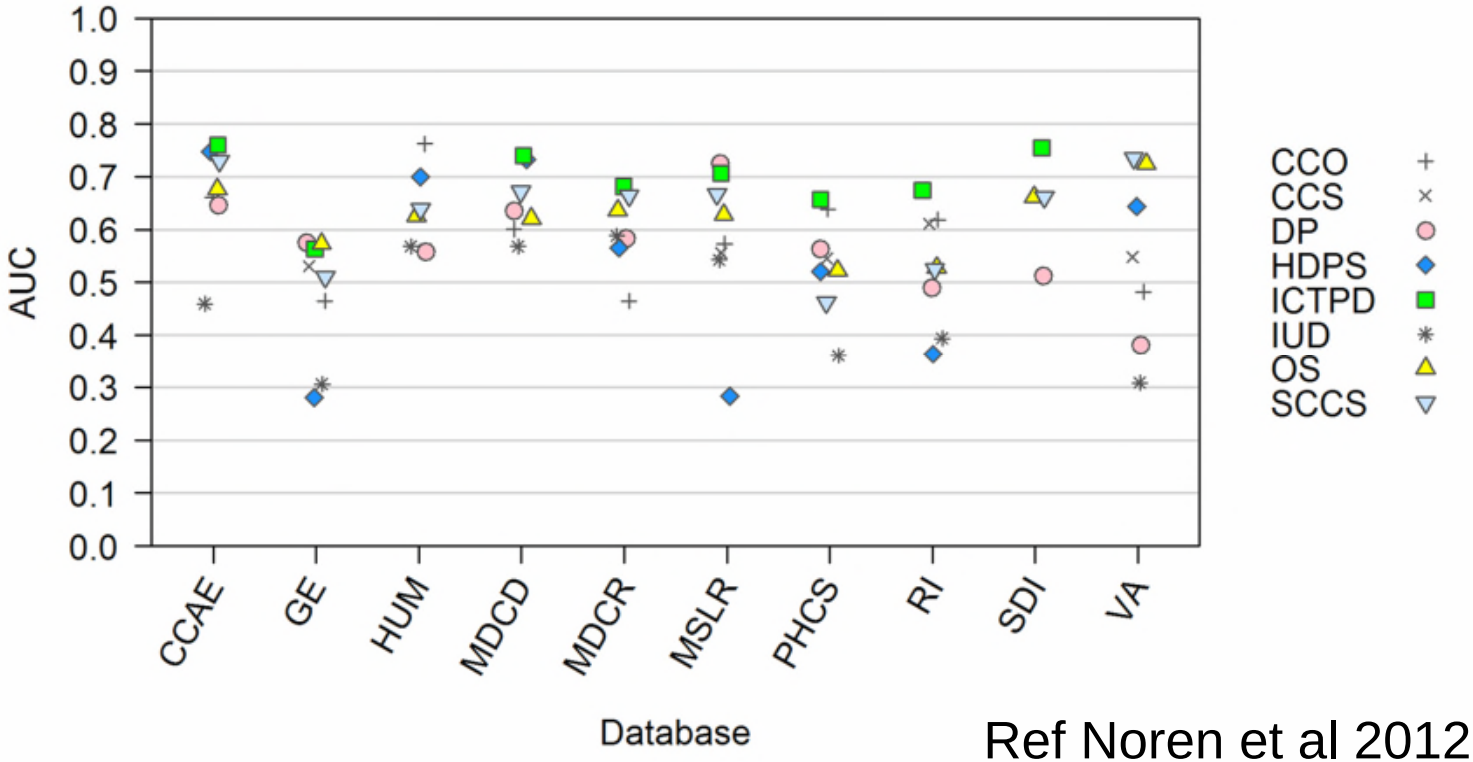
- Optimal data set(s), or combinations thereof for surveillance for specific medicinal products?
- Implications of different Data access approaches
- What are the implications of using the same data for surveillance and hypothesis testing studies?
- How to interpret scores derived from surveillance activities in observational data?
- Issues lead to extension of current research agendas and novel research agendas
  - For example the need for novel visualisation tools
- Do they work for signal detection?

# Methods tested by OMOP for surveillance

- Disproportionality Analysis (DP)
- Univariate Self-Controlled Case Series (SCCS)
- Observational Screening (OS)
- Multi-Set Case Control Estimation
- Bayesian Logistic Regression (BLR)
- Case Control Surveillance (CCS)
- IC Temporal Pattern Discovery (ICTPD)
- Case-Crossover (CCO)
- HSIU Population-Based Method
- Maximized Sequential Probability Ratio Test (MSPRT)
- High-Dimensional Propensity Score (HDPS)
- Conditional Sequential Sampling Procedure (CSSP)
- Incident User Design (IUD-HOI)

Ref Stang et al 2010 Archives of Internal Medicine

# OMOP evaluation phase I results




Ref Noren et al 2012 PDS

See also other OMOP publications

# Performance characteristics of surveiilance methods on UK EMR THIN in OMOP CDM

Results from Zhou et al 2013

| Measure | Threshold | Sensitivity | Specificity |
|---|---|---|---|
| PRR | PRR 95% LBCI >1 | 0.67 | 0.68 |
| USCCS | OR >1 and LBCI >1 (a=0.05) | 0.78 | 0.59 |
| HDPS | RR >1 and LBCI >1 (a=0.05) | 0.50 | 0.76 |

Comparison against the OMOP reference set of established drug-event combinations[1]

[1] Stang et al (2010). "Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership." Annals of Internal Medicine 153(9): 600-606.

# PROTECT Goal

PROTECT received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu).

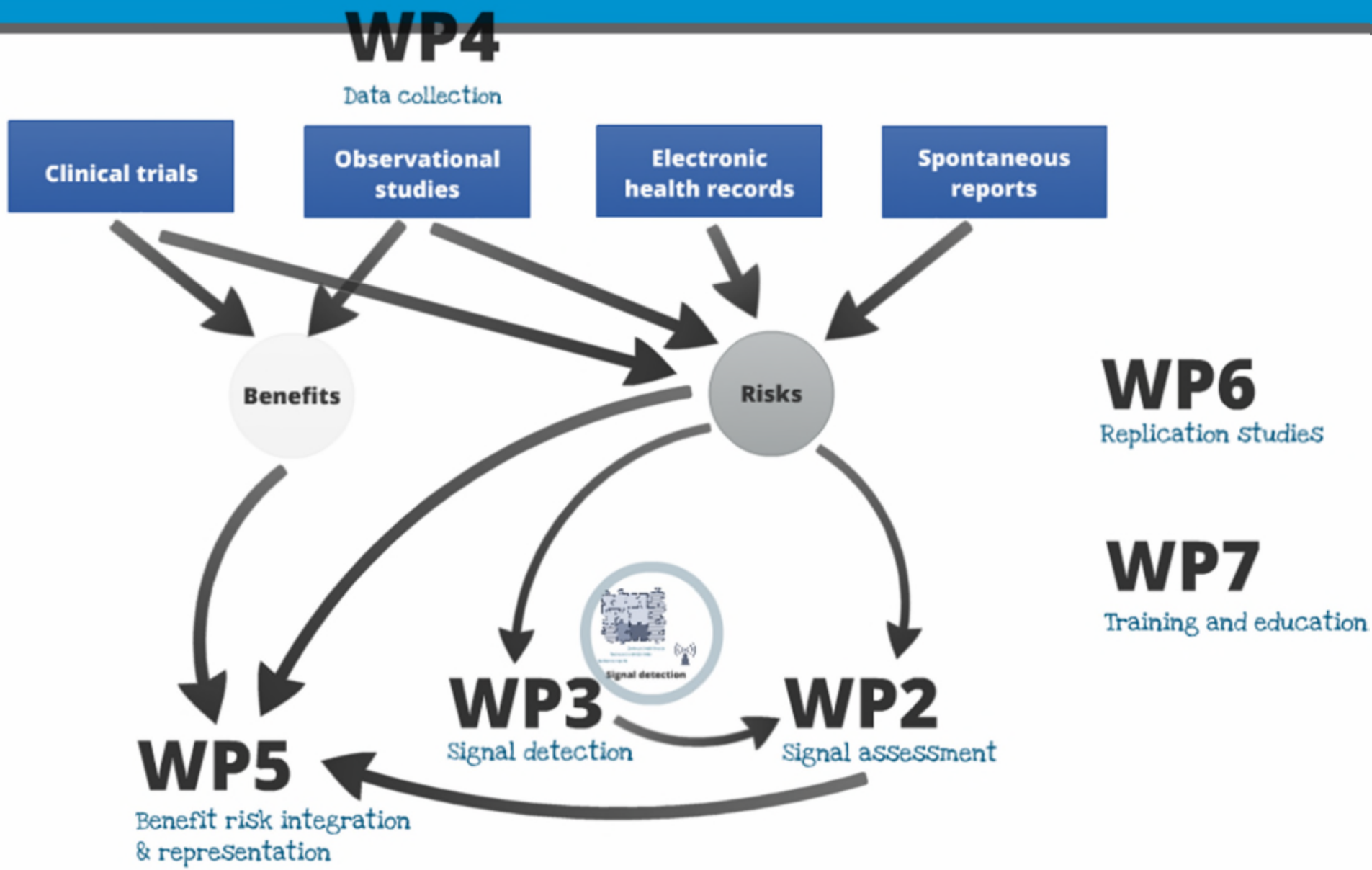
# PROTECT Goal

**To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods**

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

These methods will be tested in real-life situations.


WP4
Data collection
Clinical trials
Observational studies
Electronic health records
Spontaneous reports
Benefits
Risks
WP6
Replication studies
WP7
Training and education
Signal detection
WP3
Signal detection
WP2
Signal assessment
WP5
Benefit risk integration & representation

# Large scale systematic prospective testing of SD capability in EMR data

Results from WP3 section subpackage 10 led by Niklas Noren, UMC

Sibutramine

Nifedipine

Oedema

Flushing

**6** assessors

x

**7** drugs per assessor

x

**20** events per drug

# Preliminary results

820

# Preliminary results

820 → 509

38%

311

Not relevant terms

# Preliminary results

820 → 509 → 382

38%

311

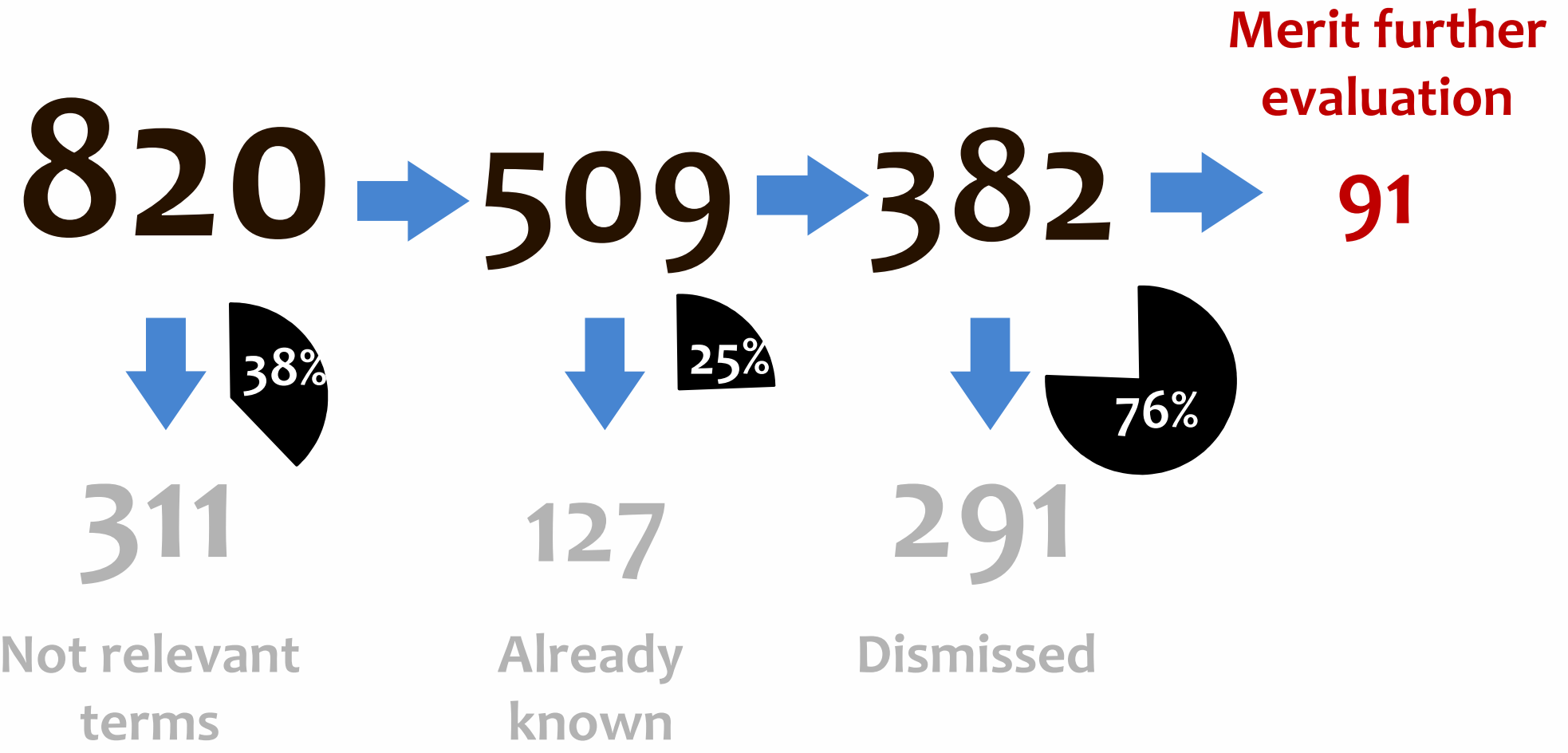
Not relevant terms

25%

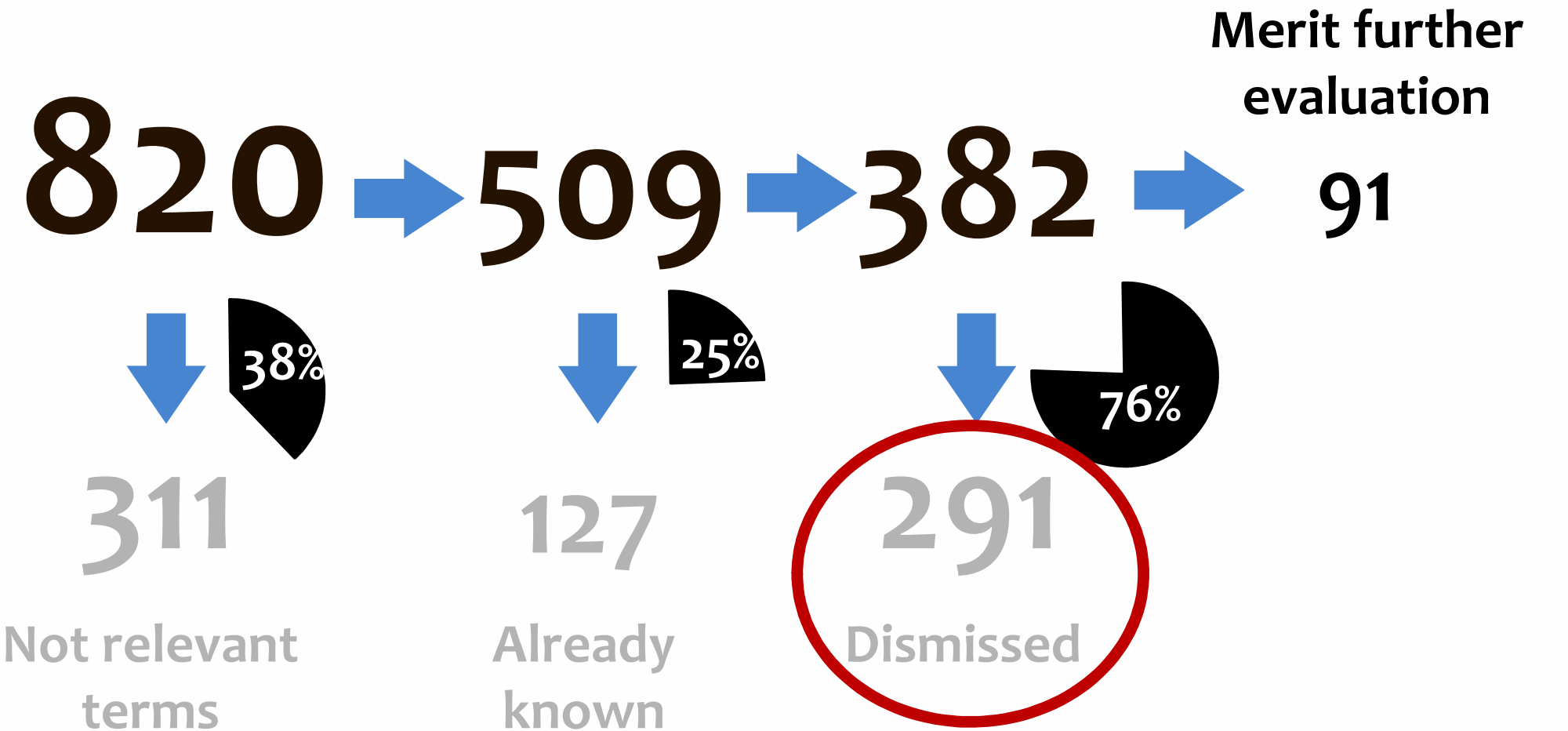
127

Already known

# Preliminary results



# Preliminary results



# Learn from previous signal detection and surveillance lessons in observational data

- Shapiro 1994 Case-Control Surveillance In Pharmacoepidemiology 3rd Edition
  - Discusses the program running since the 1970s, and in particular a false signal from the system and lessons learnt
- Walker 2002 Precautions for proactive surveillance. PDS 11(1): 17–20
  - Describes four challenges to be addressed for large scale prospective surveillance
- Carson Strom 1992 Finding unexpected effects of drugs
  - Describe thoughts and insights for surveillance processes on surveillance

# Increased Internationalization of quantitative drug safety data analysis

- PV Systems and quantitative analysis overview
  - Tomomi Kimura et al 2011 Pharmacovigilance systems and databases in Korea, Japan, and Taiwan. Pharmacoepidemiology and Drug Safety 20(12): 1237–1245
- Cohort Event Monitoring in Ghana
  - Dodoo ANO et al. 2009 Pattern of drug utilization for treatment of uncomplicated malaria in urban Ghana following national treatment policy change to artemisinin-combination therapy. Malaria Journal 8: 2
- Claims data in Korea
  - Choi NK et al 2010 Signal detection of rosuvastatin compared to other statins: data mining study using national health insurance claims database PDS 19: 238
- Renewed focus on quantitative approaches, with increased IT capability (for recording, and analyzing healthcare data)

# A tool kit for safety surveillance

- Spontaneous report analysis
- Surveillance using other data sets, such as
  - Prescription Event Monitoring
  - Clinical trial data (Pre and post marketing)
  - Health insurance claims data
  - Electronic patient and medical records
  - Utilizing established patient and/or physician networks
- For signal detection and signal refinement

Formal Epidemiological Studies will continue to play an increasingly critical role for hypothesis testing of potential safety issues

How to best combine multiple data streams for surveillance? Automated solution is not trivial

# Background reading


- Bate A & Edwards IR 2006 Data Mining in Spontaneous Reports BCPT. 98:324-330
- Brown, JS et al. 2007 Early detection of adverse drug events within population-based health networks: application of sequential testing methods. PDS 16(12): 1275-1284.
- Bate A, Evans SJW. 2009 Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety. 18(6): 427-436
- Brown JS et al. 2009. Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations. PDS18(3): 226-234.
- Stang et al 2010 Advancing the Science for Active Surveillance: Rationale and Design for the Observational Medical Outcomes Partnership 153 (9) 66-606
- Norén GN et al. 2010 Temporal Pattern Discovery in Electronic Patient Records. Data Mining and Knowledge Discovery. 20(3):361-387.
- Norén GN, et al 2012 Safety Surveillance of longitudinal databases: results on real-world data. Pharmacoepidemiology and Drug Safety 21(6) pp: 673–675
- Zhou X et al 2013 An Evaluation of the THIN Database in OMOP Common Data Model for Active Drug Safety Surveillance. Drug Safety. 36(2): 119-134
- Andersen M et al. 2014 The Asian Pharmacoepidemiology Network (AsPEN): promoting multi-national collaboration for pharmacoepidemiologic research in Asia. PDS 22: 700-704

# Conclusions

- Multiple rich heterogeneous and intricately constructed ‘real world’ data sets of observational databases
- Prospective Surveillance brings specific challenges
  - Surveillance well-established in spontaneous reports
  - Only scratching the surface in exploring the capabilities and limitations of near-real time continual scanning of databases
    - Challenging how to determine how to best utilise this wealth of data, and how to best incorporate such analyses into overall safety strategies
    - Several initiatives and partnerships doing essential foundational work in the field
- Safety surveillance is only one essential component of an overall continual assessment of benefit risk

# Question

- Which of the 4 statements below is a correct component of the CIOMS VIII definition of a signal (number 3 is true, the other 3 are false)?

1. “Information making up a signal must necessarily arise from multiple sources
2. Signal is information on a new causal association or a new aspect of a known association
3. A signal is information that suggests a new potentially causal association, and can be either adverse or beneficial in nature.
4. A signal is a statistical measure that is not judged to be of sufficient likelihood to justify verificatory action.”