Lessons from meta-analyses of Randomized Clinical Trials for Analysis of Distributed Networks of Observational Databases

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Pfizer
WORLDWIDE SAFETY & REGULATORY
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Acknowledgements and disclosure

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

Overview

- Emerging use of Real World Data in distributed data networks (DDNs)
- Examples of use
- Some comparison to RCT meta-analyses
- Conclusions

Real World Data now has a role throughout the drug development lifecycle

Discovery	Early development	Full development	Registration/ market access	Lifecycle management
How many people suffer from the condition and also have co-morbidities x and y? What drugs are currently used in the treatment of the condition and to what extent are clinical guidelines being followed?	Given efficacy and tolerability results from the early trials, how might current treatment pathways be affected with our new drug? How costly are the specific areas of unmet need that a drug with this TPP might address?	In designing the PhIII trial, what are the underlying rates of adverse events we expect to see in the trial population? Where can we modify the eligibility criteria in the PhIII protocol to reduce possible recruitment problems?	What is the likely budget impact of introducing the new drug across different patient segments? What potential safety issues do we see with the early use of the drug in practice?	How can we run a large clinical trial using EMRs to show the relative effectiveness of our drug? In which patient groups are there compliance issues with the drug?

From: Bate A et al. Designing and incorporating a Real World Data approach to international drug development and use - what the UK offers. Drug Discovery Today. In Press

Harnessing the Power of Real World Evidence for Safety

Characterize Patient Risk Profile

Evaluate Product Risks

Approval

Standing Cohorts

- EMRs
- Claims
- Registries

Active Surveillance

Monitor and detect signals in defined patient cohorts using innovative analytic methods

Post Approval Safety Studies

Compare medication risks in the real world, as prescribed and taken during routine clinical practice

Risk Minimization

Evaluate the effectiveness of risk minimization measures (e.g., product label/education)

Increasing RWD source international availability

- Some selected longitudinal 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

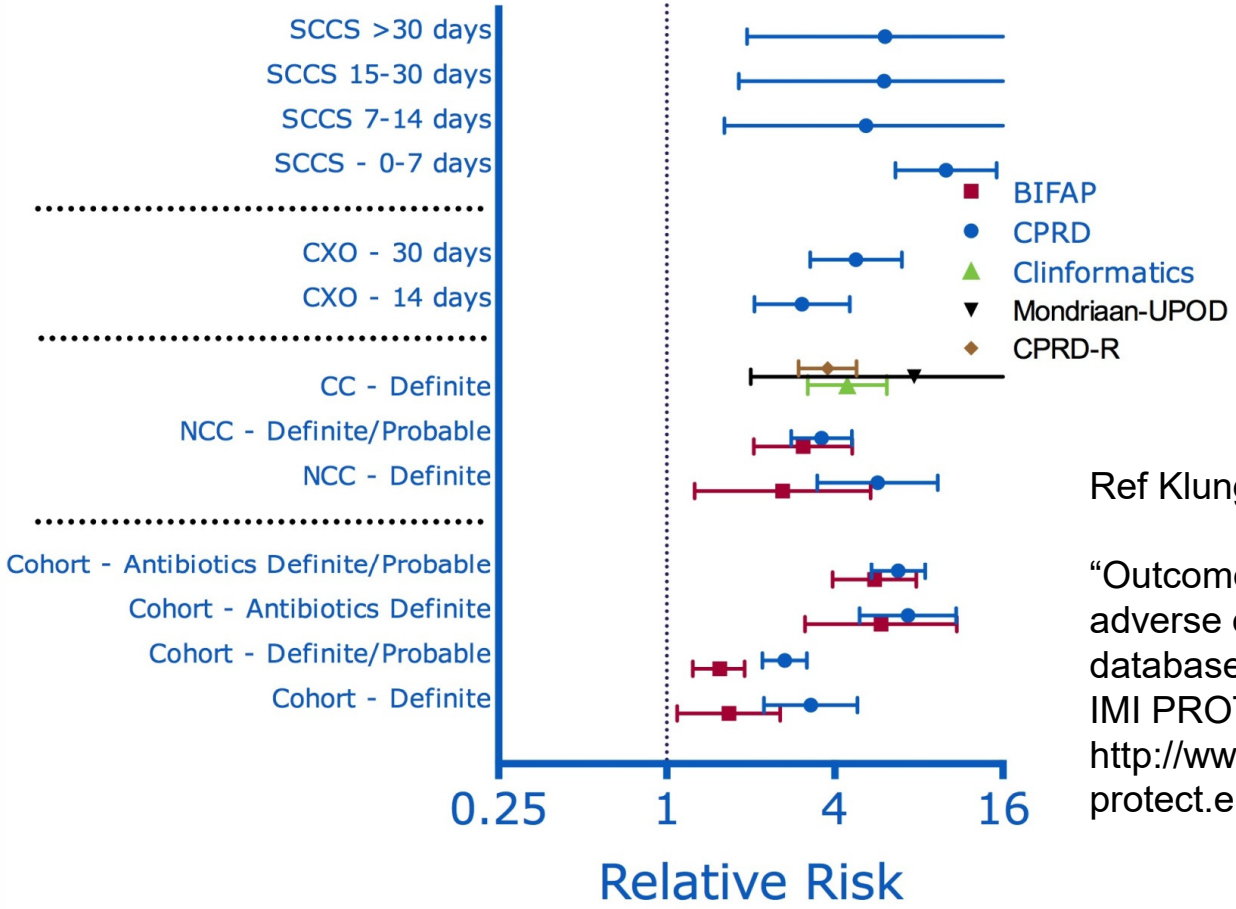
[3] Fisher BT et al. In-hospital databases In Pharmacoepidemiology 5th Edn 2011 pp 244-258

[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

Select results –Antibiotics (AB) –Acute liver injury (ALI)

AB/ALI All DBs/Designs

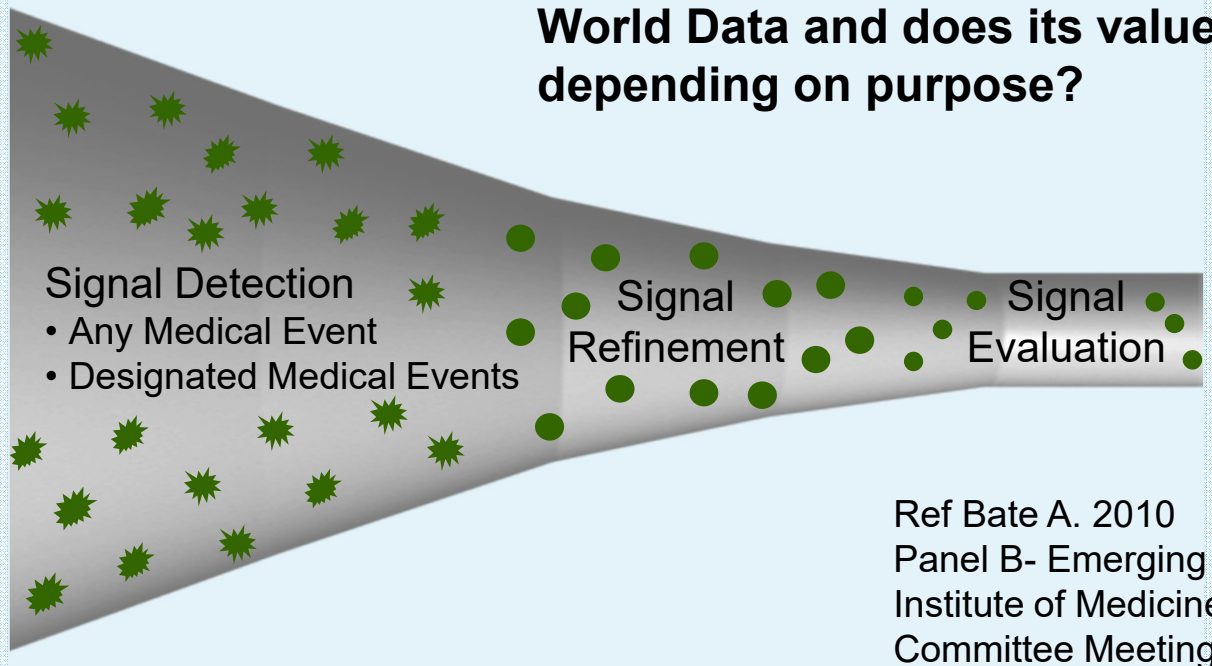


Ref Klungel OH 2015

"Outcomes of studies for six adverse event-drug pairs and five databases: what did we learn?" IMI PROTECT Symposium, London http://www.imi-protect.eu/symposium.shtml

Novel Use of longitdinal observational databases Insurance Claims & EMRs for Safety and beyond

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



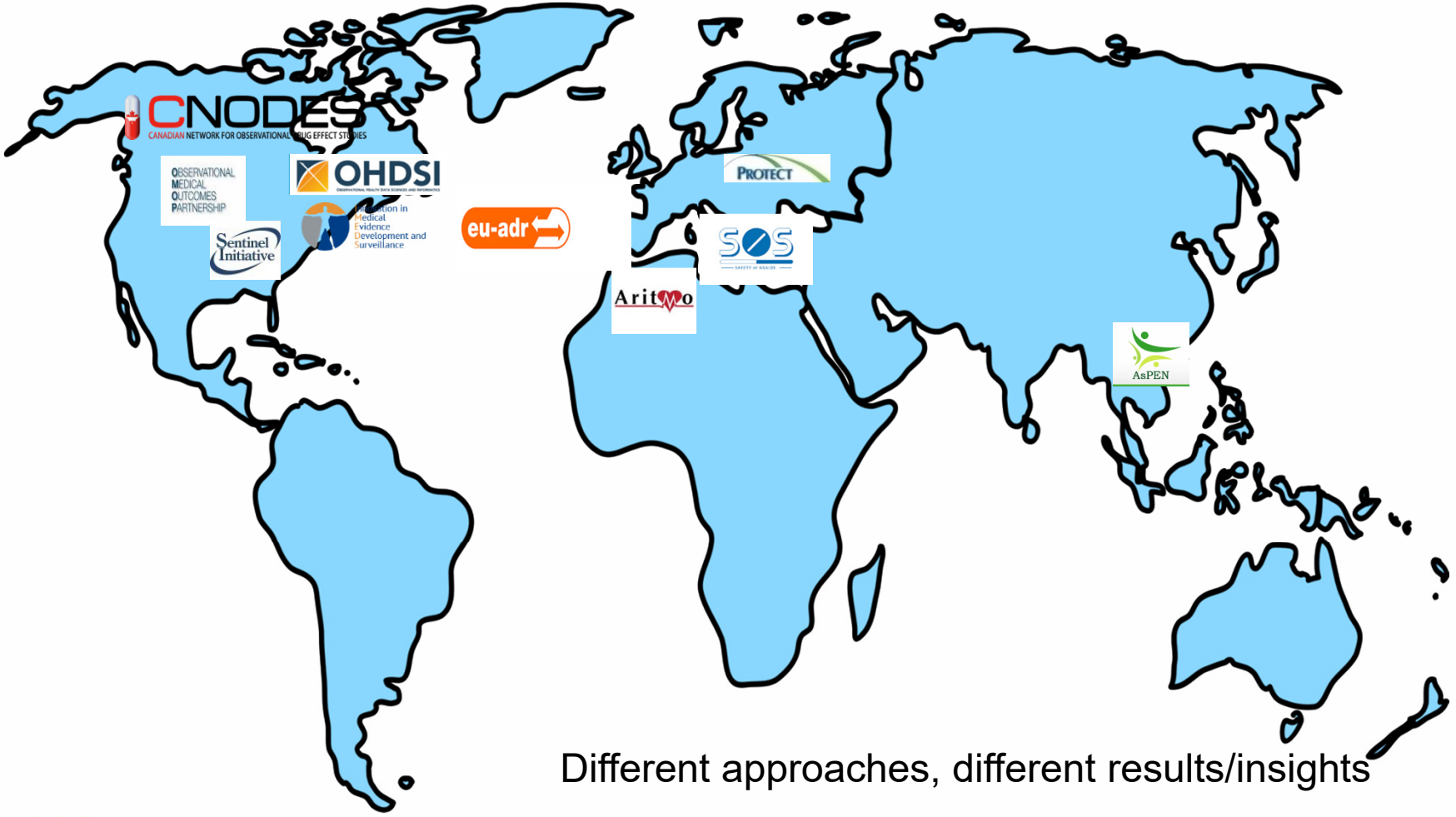
Ref Bate A. 2010
Panel B- Emerging Data Sources - Institute of Medicine (IOM) Committee Meeting, Washington DC

Product Approval & Launch

Rapid
Detect the unexpected
Less persuasive

Time Consuming
Test the anticipated
Convincing

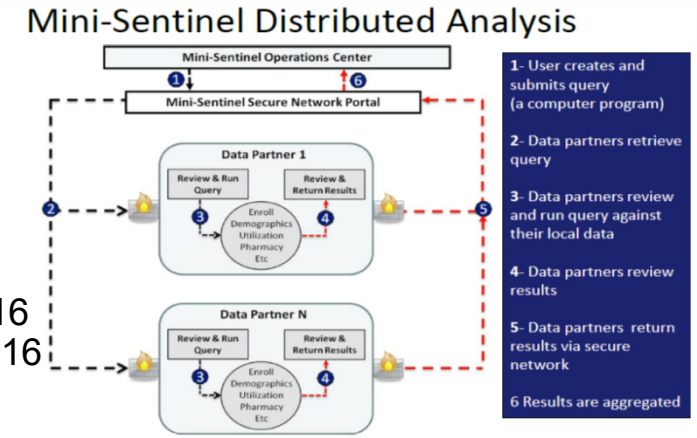
Multiple, multiple database initiatives around the world



Different approaches, different results/insights

US FDA Sentinel Initiative

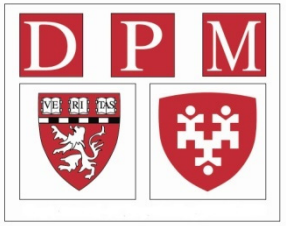
- Large Claims and EHR databases for analysis of drug outcomes, linked in “distributed network”
- Mandated by Congress: FDA Amendments Act of 2007
- Full Sentinel System now in routine use
  - Sole FDA use Mini-Sentinel Pilot project ran from 2009-2014
- Distributed database: data from 18 health plan data partners that retain physical and operational control over its own data
- Data on 193 million members
  - Rapid analysis capability



Sources: 8th Annual Sentinel Initiative Public Workshop 2016 and http://mini-sentinel.org and accessed 22nd February 2016

FDA's Sentinel Initiative
Partner Organizations

Lead – HPHC Institute



Data and scientific partners

Anthem
VANDERBILT SCHOOL OF MEDICINE
HCA Hospital Corporation of America
hmo research network
HealthCore
HUMANA
MASSACHUSETTS
OPTUM™
KAISER PERMANENTE
aetna℠

Scientific partners

UIC
OUTCOME™
Cincinnati Children's change the outcome
DukeMedicine
Penn Medicine
UAB
PARTNERS HEALTHCARE
AHIP America's Health Insurance Plans
CRITICAL PATH INSTITUTE collaborate · innovate · accelerate
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
RUTGERS Institute for Health
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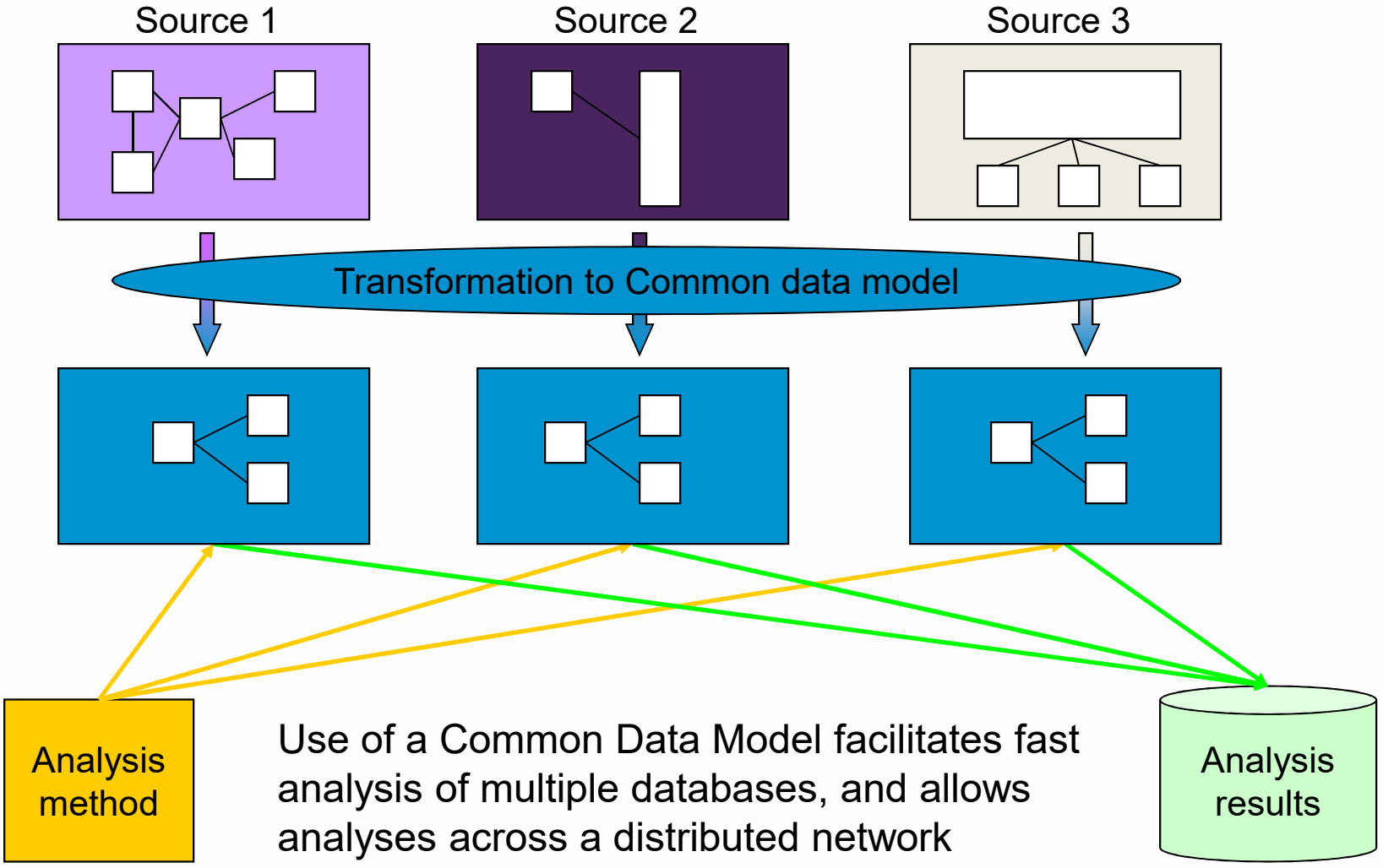
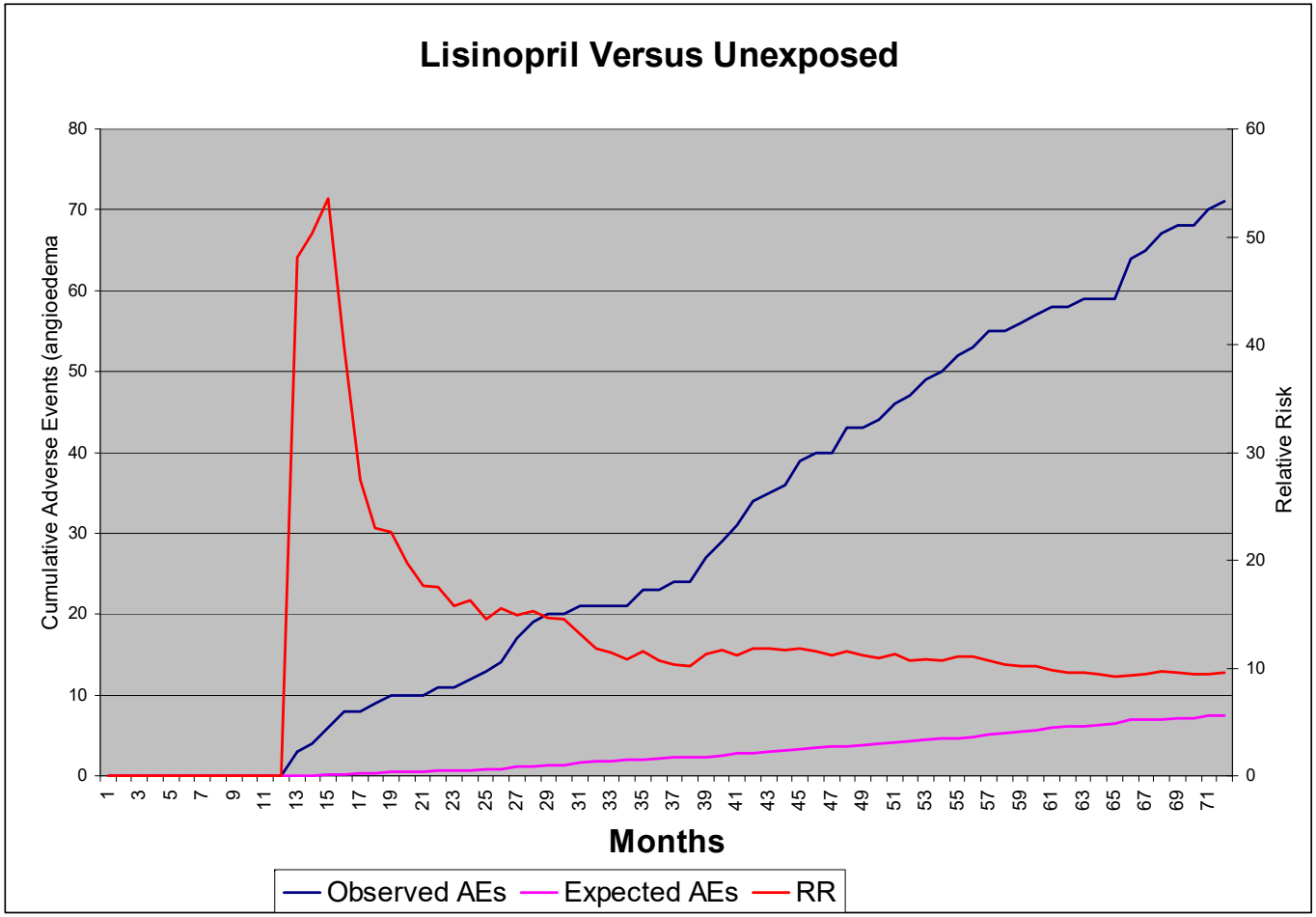
Common data model role in Analysis



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

Reference: OMOP

Rapid distributed network analysis: 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 of Disproportional Recording at month 13; 3 observed and 0.06 expected

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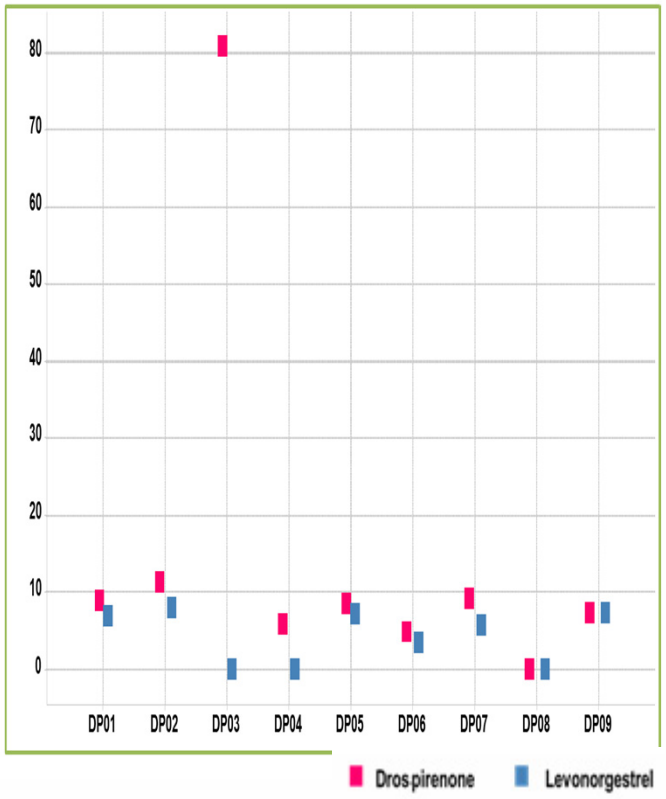
Note: Base-case analysis. Outcome: Angioedema. Adjusted for age, sex, and health plan.

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

IMEDS pilot results for OC VTE query – summary results and incidence rate by Data Partner

	4th Generation OCs	2nd Generation OCs
New Users	350,572	317,363
Dispensings	1,899,922	1,460,766
Days Supplied	62,180,487	63,102,751
Years at Risk	184,485.20	183,852.50
New Episodes w/ Events	158	121
Eligible Members	26,697,378	26,697,378
Member- Years	41768751.5	41852933.9
New Users /Eligible Members (Per 1000 members)	13.13	11.89
Days Supplied/ New User	177.37	198.83
Dispensings/ New User	5.42	4.6
Days Supplied/ Dispensing	32.73	43.2
New Episodes w/ Events /Years at Risk (Per 10000 Years)	8.56	6.58



Data Partner (DP)

RCT meta analysis compared to observational DDNs

- DDNs tend to take a general standard across network approach to data organization and structuring (e.g., the use in some networks of Common Data Models to harmonize the data structure across all datasets before analyses are conducted).
  - Beneficial due to large heterogeneity across databases in structure and makes analyses practical and efficient when multiple data set studies are required, but can be problematic in terms of data conversions to CDM and information loss
  - Cf. meta-analysis where data management is often considered at a study specific level

RCT meta analysis compared to observational DDNs – some challenges

- Across most DDNs choice of data inclusion is ‘opt in’ on the part of the database custodian – this has important implications
- Exploratory data analysis and confirmatory data analysis are often necessarily done in the same network of datasets
- Appropriate interpretation of findings and next steps in analyses from such huge networks

Background reading

- Bate A et al. Designing and incorporating a Real World Data approach to international drug development and use - what the UK offers. Drug Discovery Today. In Press
- Behrman RE et al (2011). Developing the Sentinel System—a national resource for evidence development. New England Journal of Medicine, 364(6), 498-499.
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- Cederholm S et al. 2014 Structured assessment for prospective identification of safety signals in electronic medical records: evaluation in The Health Improvement Network. Drug Safety. 38(1), 87-100.
- Stang et al (2010) Advancing the Science for Active Surveillance: Rationale and Design for the Observational Medical Outcomes Partnership Annals in Medicine 153(9), 600-6
- Walker AM, Zhou X, Ananthakrishnan AN, Weiss LS, Shen R, Sobel RE, Bate A, Reynolds RF. Computer-Assisted Expert Case Definition in Electronic Health Records. International Journal of Medical Informatics. In Press
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Conclusions

- RWD is routinely used across the drug development lifecycle
- IT developments have led to more capability and interest in conducting analyses across networks of many distinct observational 'real world' databases
  - Examples, such as the Sentinel Network, use 'distributed data networks'
- Meta-analyses has important lessons for the 'emerging scientific field' of observational DDNs from design, analysis, reporting, execution, communication and impact perspectives
  - Critically important that statisticians get involved
- Core principles similar for the two different types of analyses
  - But some differences are unavoidable – due to the nature of the data considered; and their availability and accessibility.