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

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Acknowledgements and disclosure

• Presentation is a personal perspective but contents are based on a manuscript in development “Lessons from meta-analyses of Randomized Clinical Trials for Analysis of Distributed Networks of Observational Databases” which was developed as part of an EFSPi Integrated Data Analysis: so I thank co-authors Christy Chuang-Stein, Byron Jones and Andy Roddam for their contributions.

• 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

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

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

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)

EMRs
Claims
Registries
### Increasing RWD source international availability
- Some selected longitudinal observational databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Country</th>
<th>Characteristic</th>
<th>Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>THIN UK GP primary care database</td>
<td>UK</td>
<td>GP primary care database</td>
<td>10.5 M&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Danish National Health Service Register Database</td>
<td>Denmark</td>
<td>Healthcare registry of care</td>
<td>5.5 M&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Premier US Clinical data from the hospitals</td>
<td>US</td>
<td>Clinical data from the hospitals</td>
<td>130 M+ patient discharges&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normative Health Information (NHI) Database US</td>
<td>US</td>
<td>Transactional claims records of a commercial health insurer</td>
<td>60 M&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Health Insurance Review and Assessment Service (HIRA) Korea</td>
<td>Korea</td>
<td>Insurance Claims from near universal national system</td>
<td>48 M&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> 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

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

<sup>3</sup> Fisher BT et al. In-hospital databases In Pharmacoepidemiology 5th Edn 2011 pp 244-258

<sup>4</sup> Seeger J, Daniel GW. Commercial Insurance Databases. In Pharmacoepidemiology 5th Edn 2011 pp 189-208

<sup>5</sup> 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

SCCS >30 days
SCCS 15-30 days
SCCS 7-14 days
SCCS - 0-7 days
CXO - 30 days
CXO - 14 days
CC - Definite
NCC - Definite/Probable
NCC - Definite
Cohort - Antibiotics Definite/Probable
Cohort - Antibiotics Definite
Cohort - Definite/Probable
Cohort - Definite

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

Relative Risk

0.25 1 4 16

http://www.imi-protect.eu/results.shtml
Novel Use of longitudinal 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

Signal Detection
- Any Medical Event
- Designated Medical Events

Signal Refinement

Signal Evaluation

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

FDA’s Sentinel Initiative
Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners

Optum
HCA
Aetna
Anthem
Vanderbilt School of Medicine
Humana
Massachusetts General Hospital
Kaiser Permanente

Penn Medicine
UAB
Partners Healthcare
Ohio Children’s Hospital

Critical Path Institute

UIC
Outcome

Pfizer

WORLDWIDE SAFETY & REGULATORY
Worldwide Research & Development

The University of Iowa

College of Public Health
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

Lisinopril Versus Unexposed

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

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 tools 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

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