Panel B – Emerging Data Sources and Methods for Pharmacovigilance

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Potential Conflicts of Interest statement

• Employee of Pfizer Inc
Overview

• Background
• Signal detection and analysis of spontaneous reports
  – WHO process
• Active Surveillance on EMR data: Signal identification and refinement
• Concluding remarks
Background

- Many issues driving Pharmacovigilance change including
  - More integrated, extensive Risk Management Planning
  - Risk benefit analysis method development
  - Novel Epidemiological methods, tools and approaches
    - E.g. Approaches to reduce the chance and impact of confounding
    - Public-Private partnerships and international initiatives e.g. OMOP, CIOMS
- 2007 FDAAA call for access to 100M patient records by 2012
  - FDA Sentinel Initiative to test data models and explore methods
- Existing observational databases have been routinely used for hypothesis testing for many years
  - Can they also be usefully applied to hypothesis generation? Signal detection and refinement as well as signal evaluation?
  - What is the ongoing role and value of spontaneous reports?
Routine quantitative signal detection of spontaneous reports

- Detect potential signals for further investigation that might not be readily apparent at case entry
  - Detect ‘unexpectedly’ frequent reporting relative to a background of other reports
  - Clinical review remains critical

- Several studies showing reasonable predictive value of approaches

- Used extensively, but remain areas of research

- Nature of spontaneous reports limits role in pharmacovigilance
Outline of WHO signalling procedure

- Combinations
  - Quantitative threshold
  - With quantitative information tagged

- Associations

- Signals
  - Includes triage steps

- Signals
  - Signal document

Based on Lindquist et al 2000
Data mining on spontaneous report example

Captopril - Coughing

Ref Bate1998 EJCP
Quantitative screening for duplicate case reports in anonymized data

- Novel record matching algorithm
- Some reports identical in fields but insufficiently informative data to be likely duplicates of the same report
- Algorithm detects pairs like this:

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Country</th>
<th>Drug substances</th>
<th>ADR terms</th>
<th>Onset date</th>
<th>Outcome</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>F</td>
<td>NOR</td>
<td>6 matched, 1 unmatched</td>
<td>3 unmatched</td>
<td>2004-04-30</td>
<td>?</td>
<td>+76.97</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>NOR</td>
<td></td>
<td></td>
<td>2004-04-20</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
Duplicate Detection Algorithm detects ‘over-reporting’: An example

- Three report cluster from a specific country
  - Onset: 16th Dec 2003, Females age: 8, 18 & 29
- All had same sole drug listed and sole adverse event listed; drug and AE both rare
  - Not duplicates, but all reported by the same dentist
- Statistical analysis of reports routinely assume reports are independent observations
  - Not optimal when selective ‘over-reporting’
- Such issues could lead to false positive signals
Novel Use of Claims & EMRs for signal detection/refinement

Signal Generation
- Any Medical Event
- Designated Medical Events

Signal Refinement

Signal Evaluation

Product Approval & Launch

Rapid
Detect the unexpected
Less persuasive

Time Consuming
Test the anticipated
Convincing
Some key concepts in active surveillance on Electronic Medical Records (EMRs)

• Differences between what expect and what observe after drug exposure
• Can look at events both prior and post drug exposure
• In contrast to spontaneous reports, can consider
  – Diagnoses and tests
  – Drug utilization
• Many challenges e.g. false positive findings (no clinical suspicion of causality)
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.
Acute pancreatitis recording relative to omeprazole prescription in an EMR

As presented in Noren et al 2008
Surveillance using EMRs and Claims

• Will active surveillance methods be increasingly examined on longitudinal healthcare data sets?
  – Yes

• Will they replace spontaneous reports for early signal detection in the near future?
  – No

• They might facilitate
  – Faster signal refinement
  – Better understanding for the need for formal Epidemiological studies
    • And help in study design

• Several initiatives investigating emerging roles
Some other methodological advances in safety science at Pfizer

• Issues in the use of CDMs for distributed network safety surveillance
  – Zhou X et al 2010 Lessons Learned from Mapping the THIN database to the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM). PDS 19: S311

• Clarifications around safety terminology

• Use of Large Simple Trials to study safety
  – Strom et al 2010 Comparative Mortality Associated With Ziprasidone and Olanzapine in Real-World Use Among 18,154 Patients With Schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), Am J Psych In Press

• Standing Cohorts
A Pharmacovigilance tool kit for 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
Conclusions

• Quantitative approaches add value to signal detection on spontaneous reports – and spontaneous reports do the job of signal detection well
• Pharmacoepidemiological studies for hypothesis evaluation have a crucial, routine role in drug safety
• Emerging evidence that surveillance of longitudinal observational data (EMRs and Claims databases) can contribute to process of signal detection and refinement
  – Huge challenge remains of how to separate potential true findings from vast number of false positives that could emerge
  – Much more work need to consider how to best fit emerging research into overall, routine signal management processes