Evolution of Active Surveillance: An Industry Perspective

Midwest Biopharmaceutical Statistics Workshop
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Global Patient Safety
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Outline

• US Active Surveillance Initiatives
  – Sentinel Initiative
  – Observational Medical Outcomes Partnership (OMOP)

• Other External Initiatives impacting Observational Research
  – European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
  – IMI PROTECT
  – Canada Drug Safety and Effectiveness Network
  – Asian Pharmacoepidemiology Network (ASPEN)

• Considerations for the Future

• Case Example
Observational Study Initiatives (Signal Detection / Evaluation)

AsPEN: Asian Pharmacoepidemiology Network
Other External Initiatives impacting Observational Research
The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is a project led by the European Medicines Agency intended to further strengthen the post authorisation monitoring of medicinal products in Europe by facilitating the conduct of high quality, multi-centre, independent post-authorisation studies focusing on safety and benefit-risk.
The goal of PROTECT is to strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods that will enhance the early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies), and enable the integration and presentation of data on benefits and risks.
Project Plan

The PROTECT work programme

WP7
Training & communication
WPco-L: FICF, Novartis Pharma

WP6
Validation studies involving an Extended Audience
WPco-L: PGRx (LASER), SARD

WP2
Framework for PE studies
WPco-L: UU, Pfizer

WP3
Methods for signal detection
WPco-L: UMC, BSP

WP4
New tools for data collection
WPco-L: EMEA, HU

WP5
Benefit/risk integration and representation
WPco-L: Imperial, ME

WP1
Project management & administration

Coordinator: EMEA  Deputy Coordinator: GSK
The EU-ADR project aims to develop an innovative computerized system to detect adverse drug reactions (ADRs), supplementing spontaneous reporting systems. To achieve this objective, EU-ADR will exploit clinical data from electronic healthcare records (EHRs) of over 30 million patients from several European countries (The Netherlands, Denmark, United Kingdom, and Italy). In this project a variety of text mining, epidemiological and other computational techniques will be used to analyze the EHRs in order to detect ‘signals’ (combinations of drugs and suspected adverse events that warrant further investigation).
Electronic healthcare databases for active drug safety surveillance: is there enough leverage?

**Purpose**  To provide estimates of the number and types of drugs that can be monitored for safety surveillance using electronic healthcare databases.

**Methods**  Using data from eight European databases (administrative claims, medical records) and in the context of a cohort study, we determined the amount of drug exposure required for signal detection across varying magnitudes of relative risk (RR). We provide estimates of the number and types of drugs that can be monitored as a function of actual use, minimal detectable RR, and empirically derived incidence rates for the following adverse events: (i) acute myocardial infarction; (ii) acute renal failure; (iii) anaphylactic shock; (iv) bullous eruptions; (v) rhabdomyolysis; and (vi) upper gastrointestinal bleeding. We performed data simulation to see how expansion of database size would influence the capabilities of such system.

**Results**  Data from 19,647,452 individuals (59,594,132 person-years follow-up) who used 2,289 drugs in the EU-ADR network show that for a frequent event such as acute myocardial infarction, there are 531 drugs (23% of total) for which an association with RR = 2, if present, can be investigated. For a rare event such as rhabdomyolysis, there are 19 drugs (1%) for which an association of same magnitude can be investigated.

**Conclusion**  Active surveillance using healthcare data-based networks for signal detection is feasible, although the leverage to do so may be low for infrequently used drugs and for rare outcomes. Extending database network size to include data from heterogeneous populations and increasing follow-up time are warranted to maximize leverage of these surveillance systems. Copyright © 2012 John Wiley & Sons, Ltd.
The Drug Safety and Effectiveness Network (DSEN) is being established at CIHR as part of the Government of Canada's *Food and Consumer Safety Action Plan* (FCSAP). CIHR is collaborating with Health Canada in the development of the Network, together with stakeholders from across Canada. In Canada and worldwide, there are gaps in information on the safety and effectiveness of drugs used in real-world settings. More information is needed on the safety and effectiveness of pharmaceuticals when used by diverse patient populations outside the controlled experimental environment of clinical trials. The key objectives for establishing the DSEN are to increase the available evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers and patients; and, to increase capacity within Canada to undertake high-quality post-market research in this area.

The first funding opportunity supports the creation of a single inclusive Collaborating Center for Observational Studies (CCOS) of national scope. Provincially-based researchers and data custodians would come together to allow for provincial level data to be used in nationally relevant queries of linked administrative data. DSEN is seeking a means for queries from a nationally prioritized research agenda to be applied to broad Canadian administrative data and to build research capacity Canada-wide.
FUNDED RESEARCH TOPICS

Atypical Antipsychotic Agents: comparison of outcomes that are clearly representative of the risk of breast cancer, blood dyscrasias including agranulocytosis or therapeutic effectiveness among users of different atypical antipsychotic agents.

• Given the variable increases in prolactin levels observed during treatment with atypical antipsychotic drugs, is there a corresponding increase in risk of breast cancer? What is the risk of blood dyscrasias, including agranulocytosis, among users of atypical antipsychotics? Are atypical antipsychotic drugs more effective than older agents in reducing the occurrence of hospitalization?

Drugs for Attention Deficit and Hyperactivity Disorder (ADHD): cardiovascular events among stratified age groups receiving drugs used to treat ADHD.

• Comparatively, what are the associations between rates of serious cardiovascular adverse events and drugs used to treat ADHD in Canada among stratified age groups including children between 6 and 18 years of age?

Bisphosphonates: safety and/or effectiveness of bisphosphonates.

• What is the evidence concerning the safety of bisphosphonates as they relate to atrial fibrillation and/or their effectiveness in achieving therapeutic outcomes?

Long-Acting Beta-2-Agonists (LABAs): association between serious respiratory adverse events and the use of LABAs (single ingredient vs. combination products) among stratified age groups including children.

• What is the association between serious respiratory events and the use of long-acting single ingredient beta-agonists versus combination products for the treatment of asthma across stratified age groups including children?
FUNDED RESEARCH TOPICS

Proton Pump Inhibitors (PPIs): risk of myocardial infarction among users of PPIs.
• What is the risk of myocardial infarction among users of PPIs and are these risks similar amongst various user populations?

Intravenous Immune Globulins (IVIG): risk of haemolytic anemia with different brands of IVIG.
• Are there any differences in risk of haemolytic anaemia with the different brands of intravenous immune globulin (IVIG)?

Non-steroidal anti-inflammatory drugs (NSAIDs): gaps in evidence concerning gastrointestinal or cutaneous adverse events associated with different
• What are the safety and effectiveness profiles of products within the NSAID class with respect to gastrointestinal adverse events?
• What are the safety and effectiveness profiles of products within the NSAID class with respect to cutaneous adverse events?

Drugs used by Pregnant or Lactating Women and in Paediatrics: safety and effectiveness of drugs used by pregnant and/or lactating women or in paediatric populations.
• There is a general need for information regarding safety and effectiveness of drugs used by pregnant and/or lactating women, and children. Applications will be accepted for general and investigator driven research proposals that address frequently used therapies in pregnant and nursing women and in paediatric populations for the treatment of conditions outlined in Table 1. The conditions are listed by population and each condition/population combination is considered a unique research topic.
Suggested in 3rd ACPE (Asian Conference on PE) in 2008, and presented several study results at 6th ACPE (2011)

- Constructed research collaboration network to support the conduct of cross-country pharmacoeidemiology study

- To foster links between countries to actively promote communication between academia, government, industry and consumers both at the Asia-Pacific and international level

- Ultimate goal is to develop capacity for conducting PE research in the Asian region and promote safe and effective use of medications based on the evidence produced through the quality PE studies

- Under the activities of AsPEN, if any 'signal' of particular Asian interest is found, the network of Asian researchers will co-operatively address the problem and share the information to contribute to those in charge of coping with the issue in each country get prepared for the issue.
Participating countries:

- Japan, China Taiwan, Korea, Australia, Sweden, US

AP area Database comprised:

- Japan- JMDC (Japan medical database), a claim DB, 1 million
- Taiwan- Random sample from National claim DB, 1 million
- Korea- HIRA, National claim DB, 50 million
- Australia- National Claim DB, 22 million
Example:

Multi-country study to investigate the risk of acute hyperglycaemia associated with antipsychotic use.

Results: Despite varying utilization of medicines between countries...results were similar in magnitude between countries. Olanzapine showed a trend towards increased risk in most countries, with a significant effect observed in USA medicaid population (Adjusted sequence ratio (ASR); 1.25; 95% CI 1.22-1.29, based on 20,234 pairs). Null or apparent protective associations were observed for haloperidol, quetiapine and risperidone.

Conclusion: Acute hyperglycaemia appears to be associated with olanzapine use, however, a significant effect was only observed in a very large dataset, suggesting the event is rare.
A population-based case-crossover study of polyethylene glycol use and acute renal failure risk in the elderly

We used the Korean Health Insurance Review and Assessment Service (HIRA) database that contains information on all claims including prescribed medications for approximately all 50 million Koreans. We obtained claims data for elderly patients (age 65 years or older) that had been submitted by healthcare providers based in Seoul between January 1, 2005 and December 31, 2005. Seoul is the capital and largest city of South Korea. A megacity with a population of over 12 million, it is one of the largest cities in the world. The study database contained information on 1,093,262 elderly patients with 11,842,586 prescriptions.

Conclusion: No increased risk of ARF was found in elderly PEG users.

# Observational Study Initiatives

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Sentinel/OMOP</th>
<th>EU-ADR PROTECT</th>
<th>AsPEN</th>
<th>DSEN</th>
<th>Geography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal Detection</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>US, EU</td>
</tr>
<tr>
<td>Active Surveillance</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>EU, Asia</td>
</tr>
<tr>
<td>Signal Clarification/Evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Asia, Canada</td>
</tr>
<tr>
<td>Comparative Effectiveness</td>
<td>?</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Effectiveness of Risk Minimization</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OMOP** (Observational Medical Outcomes Partnership); **EU-ADR** (system to detect adverse drug reactions); **PROTECT** (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium); **ENCEPP** European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; **AsPEN** (Asian Pharmacoepidemiology Network); **DSEN** (Canada Drug Safety and Effectiveness Network)
Considerations for the Future
What’s on Decision Makers’ Minds?

- Adverse Event Incidence
- Availability of Other Therapies
- Restricted Distribution
- Target Population
- Communication
- Treatment Effect
- Risk Management
- Medication Guides
- Trial Design and Conduct
- Nature of Disease
- Study Population
- Education
- Risk of Products In Same Class
- Trial Drop-outs
- Statistical Significance
- Labeling
- Clinical Relevance Of Endpoint
- Serious Adverse Event Incidence
- Relative Efficacy
- Expected Patient Compliance
- Off-Label Potential
- Efficacy in Subgroups
- Risk in Chronic Use
- Uncertainty
Presented by Dr Janet Woodcock, FDA Sentinel Public Workshop, Jan 2011

*Sponsors initiate and pay for queries and may include government agencies, medical product manufacturers, data and analytic partners, and academic institutions.

†Coordinating Centers are responsible for the following: operations policies and procedures, developing protocols, distributing queries, and receiving and aggregating results.
Potential Future Scope of Secondary Electronic Health Information

Medical Product Safety
- Sponsors*
  - Coordinating Center(s)†

Quality of Care
- Sponsors*
  - Coordinating Center(s)†

Biomedical Research
- Sponsors*

Public Health Surveillance
- Sponsors*

Distribution Network Governance

- Distributed Data and Analytic Partner Network
  - Payers
    - Public
    - Private
  - Providers
    - Hospitals
    - Physicians
    - Integrated Systems
  - Registries
    - Disease-specific
    - Product-specific

Common Data Model

Queries

Results

Coordinating Center(s)†

Comparative Effectiveness Research

* Sponsors initiate and pay for queries and may include government agencies, medical product manufacturers, data and analytic partners, and academic institutions.
† Coordinating Centers are responsible for the following: operations, policies, and procedures, developing protocols, distributing queries, and receiving and aggregating results.

Presented by Dr Janet Woodcock, FDA Sentinel Public Workshop, Jan 2011
Active Surveillance Using Observational Data

**Value**
- Detect new signals sooner (“real-time”)
- Establishing safety profile (lack of signal)

**Concerns**
- Address false positives
- Workload due to false positives
- Data interpretation & communication

**Stakeholder Needs**
- Continue to realize value of traditional PhV and importance of medical judgment
- Best practices: signal detection and evaluation methodology using observational data
- Guidances: how to best utilize observational data for active surveillance
- Communication plans: how, when and to whom to communicate findings
Active Surveillance Plan for a Marketed Product
Overview of Marketed Product-X (MP-X) Active Surveillance

- The primary objective is to screen for possible safety signals in real world settings using a large US insurance claims database by comparing the incidence rates of events among LABELLED INDICATED patients treated with MP-X vs COMPARATOR Y (COMP-Y)

- It is intended to complement routine surveillance
  - A safety signal is defined as a drug-event combination that exceeds a point estimate of: $HR \geq 2$ with a lower 95% CI of $\geq 1$
  - Identified signals will be medically evaluated following Company’s pharmacovigilance processes
## Unique Challenges

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Commercially-Available Options</th>
<th>Our Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple unique inclusion and exclusion criteria were needed to define the cohort (eg. having a diagnosis of OUTCOME-Z within 5 days prior to the index date and having a PROCEDURE-Y 5 days prior to or 10 days after INDICATION Dx)</td>
<td>Not flexible enough to fully define the at-risk population</td>
<td>Utilize in-house analytical capabilities to customize cohort creation in SAS</td>
</tr>
<tr>
<td>Evaluation of a large number of events</td>
<td>Capable</td>
<td>Automated covariate selection to create a ‘customized’ propensity score for each event</td>
</tr>
<tr>
<td>Each event may have different risk factors</td>
<td>Evaluation at cohort level only</td>
<td></td>
</tr>
</tbody>
</table>
Study Design

• Retrospective cohort study using a large admin claims database
• Measures taken to ensure the comparability of the two drug cohorts
  – The two drugs are from the same class
  – The comparative analyses are conducted among patients with the same indication for both drugs while controlling for imbalanced baseline patient differences
• Signal detection initiated once 1000 patients received MP-X
Study Population - Inclusion Criteria

– Must have at least one prescription for MP-X vs COMP-Y after defined date
  • First prescription = index date
– Must be at least 18 years of age
– Must have been enrolled in the insurance plan for at least 6 months prior to the index date
Baseline Patient Characteristics

- Compares counts of MP-X and COMP-Y patients with baseline events, medications, health care utilization metrics and other demographic variables
- Provided to supplement the active surveillance output

### Table 1.
Baseline Demographic and Clinical Characteristics in MP-X and COMP-Y Initiators
HealthCare Database 1 through Q12012

<table>
<thead>
<tr>
<th>Baseline Characteristic (Within 8 months Prior to Index)</th>
<th>MP-X</th>
<th>COMP-Y</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Index, mean +/- SD in years (N)</td>
<td>67 +/- 9</td>
<td>62 +/- 12</td>
<td>0.00000</td>
</tr>
<tr>
<td>Age at Index Range (Narrow) in years (Range)</td>
<td>18-24</td>
<td>203 (6)</td>
<td>203 (6)</td>
</tr>
<tr>
<td></td>
<td>25-44</td>
<td>205 (8)</td>
<td>2.00 (6.3)</td>
</tr>
<tr>
<td></td>
<td>45-54</td>
<td>3.15 (29.7)</td>
<td>3.04 (24.1)</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>4.88 (58.6)</td>
<td>4.98 (78.5)</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>1.44 (12.3)</td>
<td>7.10 (17.3)</td>
</tr>
<tr>
<td></td>
<td>75-84</td>
<td>2.08 (16.8)</td>
<td>6.08 (14.0)</td>
</tr>
<tr>
<td></td>
<td>85+6</td>
<td>0.00 (0)</td>
<td>1.80 (3.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Characteristic (Within 8 months Prior to Index)</th>
<th>MP-X</th>
<th>COMP-Y</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Index Range (Wide) in years (Range)</td>
<td>&lt;75</td>
<td>10.47 (87.5)</td>
<td>37.25 (82.3)</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>207 (25)</td>
<td>8,005 (97.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>MP-X</th>
<th>COMP-Y</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2.335 (21.6)</td>
<td>13.370 (29.5)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Male</td>
<td>2.652 (78.2)</td>
<td>21.501 (70.5)</td>
<td>0.00000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History</th>
<th>MP-X</th>
<th>COMP-Y</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDICATION Dx</td>
<td>10,679 (100.0)</td>
<td>45,277 (100.0)</td>
<td>.</td>
</tr>
<tr>
<td>Medical Hx Dx+</td>
<td>311 (2.9)</td>
<td>2,075 (4.8)</td>
<td>0.00005</td>
</tr>
<tr>
<td>Medical Hx Dx&lt;</td>
<td>487 (4.3)</td>
<td>3,778 (8.3)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Medical Hx Dx=</td>
<td>43 (0.4)</td>
<td>373 (0.8)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Medical Hx DxX</td>
<td>2,503 (24.2)</td>
<td>12,119 (26.8)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Medical Hx Dx-</td>
<td>1,255 (11.3)</td>
<td>6,305 (13.8)</td>
<td>0.00000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>MP-X</th>
<th>COMP-Y</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant Med1</td>
<td>2.388 (22.2)</td>
<td>9.683 (21.8)</td>
<td>0.38328</td>
</tr>
<tr>
<td>Concomitant Med2</td>
<td>452 (4.3)</td>
<td>2,165 (4.8)</td>
<td>0.05238</td>
</tr>
<tr>
<td>Concomitant Med3</td>
<td>86 (0.6)</td>
<td>8,144 (1.8)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Concomitant Med4</td>
<td>2.878 (27.0)</td>
<td>13,297 (29.4)</td>
<td>0.00000</td>
</tr>
<tr>
<td>Concomitant Med=</td>
<td>1.491 (14.0)</td>
<td>8,104 (17.9)</td>
<td>0.00000</td>
</tr>
</tbody>
</table>
Key Steps in Active Surveillance-Signal Detection

• Assemble a list of all events (post-index diagnoses) in the study population

• For each event:
  – Calculate a propensity score for each patient
    • Covariates are identified by:
      – Pre-determined list of variables of interest: age, sex, index quarter, region, healthcare utilization variables
      – An automated covariate selection technique which chooses the most influential covariates from all of the baseline diagnoses, procedures and medications of those who did not have the event during baseline

    – Group patients into strata (quintiles) by propensity score
    – Calculate incidence rates and hazard ratios

• Assess imbalance by events and overall and adjust model as necessary
### Active Surveillance- Signal Detection Output (Sample)

#### Table 2. MP-X Active Surveillance Results - All Outcomes

Evaluation based on MP-X and COMP-Y Initiators with INDICATION Dx

Rates are Adjusted Using a High-Dimensional Propensity Score Methodology

HealthCare Database 1 through Q12012

<table>
<thead>
<tr>
<th>Outcome of Interest (COI)</th>
<th>MP-X</th>
<th>COMP-Y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Counts</td>
<td>Incidence Rate (per 1000 Pat.Yrs)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>With OOi</td>
</tr>
<tr>
<td>181 Other complications of pregnancy</td>
<td>10679</td>
<td>5</td>
</tr>
<tr>
<td>227 Spinal cord injury</td>
<td>10679</td>
<td>6</td>
</tr>
<tr>
<td>668 Personality disorders</td>
<td>10679</td>
<td>7</td>
</tr>
<tr>
<td>79 Parkinson's disease</td>
<td>10679</td>
<td>7</td>
</tr>
<tr>
<td>240 Burns</td>
<td>10679</td>
<td>14</td>
</tr>
<tr>
<td>135 Intestinal infection</td>
<td>10679</td>
<td>61</td>
</tr>
<tr>
<td>77 Encephalitis (except that caused by tuberculosis)</td>
<td>10679</td>
<td>2</td>
</tr>
<tr>
<td>8 Other infections, including parasitic</td>
<td>10679</td>
<td>49</td>
</tr>
<tr>
<td>224 Other perinatal conditions</td>
<td>10679</td>
<td>6</td>
</tr>
</tbody>
</table>
## Active Surveillance - Strengths and Limitations

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complements routine surveillance by providing more details about</td>
<td>Current lag time is 11 months with Database. For a new drug with slow uptake it may take a long time to accumulate data</td>
</tr>
<tr>
<td>• Patients characteristics</td>
<td>• Dispensing record is not equal to patient’s actually consuming the drug</td>
</tr>
<tr>
<td>• Drug usage over time</td>
<td>• Key information missing (eg body weight)</td>
</tr>
<tr>
<td>Advantages over commercial packages</td>
<td></td>
</tr>
<tr>
<td>• Propensity score customized for every drug-event pair vs a ‘one-size-fits-all’ approach</td>
<td></td>
</tr>
<tr>
<td>• Allows for the customization of disease state (eg. INDICATION Dx/PROCEDURE-Y ) in defining drug cohorts</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions – Active Surveillance Initiatives

- New active surveillance initiative evolving
- Tool in the “toolbox”
- Should not be used in isolation, supplement to traditional pharmacovigilance methods
- Not a substitute for medical judgment
- Challenges will need to be addressed (e.g., false positive rate)
- Central need for guidances and best practices
- Efficient and effective communication strategy