Harnessing the Power of Real-World Data for Safety Surveillance

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Disclosure and Acknowledgements

• Jamie Geier is an employee and shareholder of Pfizer, Inc. The opinions expressed in this presentation are not necessarily those of Pfizer, Inc.

• Acknowledgements:
  – Pfizer Colleagues from Worldwide Safety & Regulatory as well as Statistics
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Understand the evolving role of traditional Epidemiologic data sets within the pharmacovigilance landscape

Share best practices and learnings from our experience working with real-world data at Pfizer

Consideration of how to integrate new signal detection approaches using real-world data to protect and promote public health

PV= pharmacovigilance
Safety Evaluations are Conducted and Refined Throughout a Product’s Lifespan

Safety Activities from First In Human through Post-Authorisation
(Safety & Regulatory Focus Through Product Lifespan)

FIH=first in human; IND=investigational new drug; POC=proof of concept; REMS=risk evaluation and mitigation strategies, RMMs=risk minimisation measures
Adapted from Caubel P, Australia PV Conference ARCS 23Aug2018.
# Real-World Evidence in a Pharma Context

Insights on diseases, products, and patient populations derived from the analysis of “real world” data – beyond controlled trials

<table>
<thead>
<tr>
<th>Data</th>
<th>Methodologies</th>
<th>Insights</th>
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<tbody>
<tr>
<td>Anything other than data from a randomized controlled trial that permits longitudinal observation</td>
<td>Structured approach to data analysis and generation of meaningful impacts</td>
<td>Innovative, value adding information about products, patients or competitive landscape</td>
</tr>
</tbody>
</table>
| - Claims databases  
- Registries/observational trials  
- Prospective cohort  
- Lab data  
- Clinical records  
- Genomic data | - Prospective Non-Interventional Research (NIR)  
- Retrospective database analysis  
- Econometric modelling | - Comparative effectiveness  
- Safety  
- Health economics  
- Care pathways  
- Comparative therapy insights  
- … and many more |
The Epidemiologist’s Tool Kit: Virtual Cohorts for Risk Characterisation, Safety and Effectiveness Surveillance

Characterise Patient Risk Profile

Evaluate Medication Risk

Virtual Patient Cohorts

Rapid Queries
Estimate expected risks in indicated populations

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 Minimisation
Evaluate the effectiveness of risk minimisation measures (e.g., label/education)

Approval
Minimum amount of tofacitinib exposure (PY) required to detect a significant difference of 1.5x and 2.0x vs a bDMARD comparator in relation to example background event rates

Tofacitinib data based on March 2015 data cut. There were 21,199 PY of tofacitinib exposure as of January 2016.

AE=adverse event; bDMARD=biologic disease-modifying antirheumatic drug; GI=gastrointestinal; IR=incidence rate; LTE=long-term extension; MACE=major adverse cardiovascular event; NMSC=non-melanoma skin cancer; PY=patient-year; OI=opportunistic infection; RA=rheumatoid arthritis; SIE=serious infection event.

# A Selection of Healthcare Databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Country</th>
<th>Characteristic</th>
<th>Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>THIN</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</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</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)</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>

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 5<sup>th</sup> Edn 2011 pp 244-258
4 Seeger J, Daniel GW. Commercial Insurance Databases. In Pharmacoepidemiology 5<sup>th</sup> Edn 2011 pp 189-208
5 Kimura T et al. Pharmacovigilance systems and databases in Korea, Japan and Taiwan. PDS. 2011; 20: 1237–1245
The Effectiveness of the Xeljanz RMM is Measured Using a Dual-Evidence Approach with Complementary Data Sources¹, ²

**Process Indicators**

- aRMM Material Distribution metrics (aRMM program implementation)
- Assessment of Prescriber aRMM materials receipt, knowledge of key risk messages and self-reported adherence to recommended RM practices
  - A cross-sectional multimodal survey among prescribers of Xeljanz
  - Conducted in 8 EU countries
- Assessment of Clinical Action
  - DUS via existing electronic health records
  - Prescribing trends linked to clinical and demographic data

**Outcome Indicators**

- ADR occurrence / severity
  - Contextualization via synthesis of published literature (CT or observational studies) and non-proprietary SRS
  - Analyses via Spontaneous Report Systems
  - Prospective evaluation of risks through an established US and 4 EU RA registries
  - Prospective evaluations of risks within the DUS framework

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aRMM=additional risk minimisation measures; CT=clinical trial; DUS=drug utilisation study; EU=European Union; RMM=risk minimisation measures; US=United States
Longitudinal observational data

+ Denominators

- No clinical suspicion

Longitudinal

“Objective”

Data not collected for causality assessment

Restricted scope

Credit: GN Norén
Methodological Advances Tested by Pfizer for Signal Detection Show Promise

- **Disproportionality Analysis (DP)**

- **Self-Controlled Case Series (SCCS)**

- **Tree Based Scan Statistic (TBSS)**

- **Sequential methods**

- **IC Temporal Pattern Discovery (ICTPD)**

- **IC Temporal Pattern Discovery (ICTPD) + Disturbance Algorithm**
Processes Implementing New Methodologies for Signal Detection Hold Promise for Connecting with other PV Activities (including SRS data)

Disturbance Algorithm

Signals of Disproportionate Recording (SDR)

- Chronographs + Data for all Combinations
- Chronographs + Data for all Combinations
- Chronographs + Data for all Combinations

Database 1

Database 2

Database 3

Outcomes of Potential Interest (MedDRA Terms)

Terminological Conversions

Subject Matter Expert Review of Outlier Subset

Clinical Review by Product Safety Risk Lead

Further use of CVW Longitudinal tool & rapid analyses via internal analytic tools.

Signals of Suspected Causality (Risk Management Committee, etc)

Signal Refinement Activities

TBD (case-by-case basis)

Bridging to routine & enhanced PV work

* Definitions for all abbreviations are within the notes section of the slide.
Methodological Advances: High Throughput Screening of Chronographs

• Chronographs
  – Visual tool to show changes in a disproportionality measure (IC) over time
  – Stratified into pre/post exposure windows

• Disturbance Algorithm
  – ARIMA based time-series methodology with structured outlier analysis
  – Finds “disturbances” that occur outside the normal pattern trends

ARIMA=autoregressive integrated moving average; IC=information component
Note: An additive outlier indicates an immediate impact of drug effect with no residual activity. A temporary change indicates a lingering effect but not the lasting effect of a level shift.
Experience Gained in the 4 Tenets Critical for Advancing Signal Detection Capabilities

- **Data**
  - Leveraged in house databases including US Claims, US EMR & UK EMR
  - 4 Therapies

- **Methods**
  - Implemented & gained prospective experience with ICTPD
  - Poised to formally evaluate other methodologies, as the field evolves

- **Processes**
  - Developed a scalable & effective approach
  - Connects seamlessly to routine signal detection of other data streams, including SRS data

- **Tools**
  - Software validated for safety assessments

EMR=Electronic Medical Records; ICTPD=Information Component Temporal Pattern Discovery; UK=United Kingdom; US=United States
Signal Detection in RWD holds promise
- Benefits are not yet fully articulated
- Potential complementary role to other data streams (i.e., spontaneous reports, social media efforts, etc.)

Expectations are high
- Regulatory application important
- Routine application to enhance signal detection capabilities is timely
- Find solutions to bigger problems
  - Predictive capabilities
  - Near “real time” assessments
  - Lessening of colleague burden
  - Strengths and limitations of varied methodologies

How can we as a community work together to articulate the “promise” of these data to ensure a positive impact of their use across our field?
Emerging Guidance Enhances the Robust Use of RWD

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making
Hypothesis-Free Signal Detection in EHR Data

Useful Interplay Between Spontaneous ADR Reports and Electronic Healthcare Records in Signal Detection


Key Points

- Overall, a spontaneous reporting system (SRS) is better suited to detection of signals than an electronic health record (EHR)-based system, especially for certain types of reactions (rare events and those with a high drug-attributable risk).

- Use of EHRs might be justifiable in some situations where SRSs perform poorly (e.g. outcomes with a high background incidence), provided that the additional costs can be taken into account.

SRSs and EHR-based signal detection systems can be complementary, the additional value of one to the other varying across events, as a function of the background incidence of the event.
Thank you.