Risk Characterisation Utilising External Data Sources: A Methodological Consideration for Clinical Trials with High Subject Drop-Out

An Industry Perspective

Jamie Geier, PhD
Senior Director Epidemiology
Pfizer, Inc.
Disclosure

• Jamie Geier is an employee and shareholder in Pfizer, Inc. The views expressed in this presentation do not necessarily represent those of Pfizer.
Risk Characterisation & Industry

• Epidemiology & Industry
  – Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC)
  – Varenicline (Chantix®)

• The Application of “Virtual Cohorts”

• Lessons Learned

ZODIAC=Ziprasidone Observational Study of Cardiac Outcomes
Ziprasidone is an atypical antipsychotic treatment launched September 2000 in Sweden and March 2001 in the United States

– Modestly prolongs the QTc interval, but whether this has important clinical relevance was not known
– Lower incidence of weight gain reported in clinical trials when compared with other antipsychotics
– Potentially beneficial changes in lipid profiles observed with treatment in clinical development programme

Question of interest to regulators at the time of approval: Does use of ziprasidone in the “real world” increase the risk of clinically meaningful, serious cardiovascular events?
ZODIAC: Methodology

• An international, multicenter, observational study with randomization to compare the cardiovascular safety of ziprasidone and olanzapine

• Study design is “Large Simple Trial”
  – Large, naturalistic, prospective study with random assignment of patients to antipsychotic treatment, to control for channeling bias
  – 18,154 patients randomised to ziprasidone or olanzapine
  – No additional study-required monitoring or tests after randomisation
  – Follow-up during usual care for 1 year

• Both agents to be used as per local product labeling (USPI, SPC etc.)
  – Ziprasidone 40 mg/day starting dose in the United States, 80 mg/day in other countries; maximum 160 mg/day
  – Olanzapine 5-20 mg/day

mg=miligrams; SPC= Summary of Product Characteristics; USPI=United States Product Insert
ZODIAC: Design

Inclusion criteria based on local label

- Ziprasidone N = 9,000
  - Mortality or hospitalization
- Olanzapine N = 9,000
  - Mortality or hospitalization

BASELINE: Patients are randomly assigned treatments (Interactive voice response system, telephone procedure)

Normal clinical course

Status assessments every 2-3 months for 1 year

Follow-up period

Patient visits psychiatrist

Study ends

FINAL ASSESSMENT
ZODIAC: Global Enrollment in 18 Countries

Total Patient Enrollment = 18,154 patients from 749 sites
## ZODIAC: Mortality Endpoint Results

<table>
<thead>
<tr>
<th>Mortality endpoint</th>
<th>Ziprasidone (n= 9,077) n (%)</th>
<th>Olanzapine (n=9,077) n (%)</th>
<th>Relative Risk (95% CI)</th>
<th>Total (N=18,154) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-suicide mortality*</td>
<td>83 (0.91)</td>
<td>81 (0.90)</td>
<td>1.02 (0.76, 1.39)</td>
<td>164 (0.90)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>103 (1.13)</td>
<td>102 (1.12)</td>
<td>1.01 (0.77, 1.33)</td>
<td>205 (1.13)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>2 (0.02)</td>
<td>3 (0.03)</td>
<td>0.67 (0.11, 3.99)</td>
<td>5 (0.03)</td>
</tr>
<tr>
<td>Cardiovascular mortality†</td>
<td>3 (0.03)</td>
<td>8 (0.09)</td>
<td>0.38 (0.10, 1.41)</td>
<td>11 (0.06)</td>
</tr>
<tr>
<td>Suicide mortality</td>
<td>19 (0.21)</td>
<td>16 (0.18)</td>
<td>1.19 (0.61, 2.31)</td>
<td>35 (0.19)</td>
</tr>
</tbody>
</table>

*One death in the ziprasidone group met criteria for both non-suicide and suicide mortality.

† When events classified by Endpoint Committee as cardiovascular mortality with insufficient data conservatively added to definite and possible events, RR = 1.60 (95% CI: 0.84, 3.05) for ziprasidone vs. olanzapine.
ZODIAC: Readjudication of the Secondary Endpoint of Sudden Death, Three Domains

- **Witness**
  - Witnessed
  - Not Witnessed
  - Insufficient / No Information

- **Timing**
  - ≤ 1 hour
  - >1 hour to ≤ 24 hours
  - > 24 hours
  - Insufficient / No Information

- **Cause**
  - Cardiac arrhythmia (non-conduction disorder)
  - Cardiac arrhythmia (conduction disorder)
  - Myocardial Infarction
  - Other cardiac cause
  - Non-cardiac cause
  - Unknown
<table>
<thead>
<tr>
<th>Sudden Death Endpoints</th>
<th>Ziprasidone (n= 9,077) n (%)</th>
<th>Olanzapine (n=9,077) n (%)</th>
<th>Relative Risk (95% CI)</th>
<th>Total (N=18,154) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death (original)</td>
<td>2 (0.02)</td>
<td>3 (0.03)</td>
<td>0.67 (0.11, 3.99)</td>
<td>5 (0.03)</td>
</tr>
<tr>
<td>NOS (R96 or R96.1 or I46.1)</td>
<td>9 (0.1)</td>
<td>8 (0.1)</td>
<td>1.11 (0.45-2.77)</td>
<td>17 (0.1)</td>
</tr>
<tr>
<td>Sensitivity Analyses (R96 or R96.1 or I46.1 or R98 or R99)</td>
<td>20 (0.2)</td>
<td>27 (0.3)</td>
<td>0.73 (0.44-1.22)</td>
<td>47 (0.3)</td>
</tr>
<tr>
<td>NOS (R96 or R96.1)</td>
<td>6 (0.1)</td>
<td>5 (0.1)</td>
<td>1.19 (0.37-3.77)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Cardiac Death (I46.1)</td>
<td>3 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
<td>0.99 (0.20-4.79)</td>
<td>6 (&lt;0.1)</td>
</tr>
<tr>
<td>Sensitivity Analysis (R96 or R96.1 or I46.1 or R98 or R99 or “Other”)</td>
<td>31 (0.3)</td>
<td>31 (0.3)</td>
<td>0.99 (0.65-1.50)</td>
<td>62 (0.3)</td>
</tr>
</tbody>
</table>

ICD-10= International Classification of Diseases and Related Health Problems, 10th Revision; NOS=not otherwise specified
ZODIAC: Conclusions

• ZODIAC is the largest randomised study of patients with schizophrenia conducted to date

• Readjudication of the sudden death endpoint according to ICD 10 criteria yielded results consistent with the study’s initial findings
  – Sudden death NOS (RR=1.11, 95% CI: 0.45-2.77)
  – Sensitivity analyses (RR=0.73, 95% CI: 0.44-1.22)

• Supplemental analyses showed no difference in the risk of sudden death comparing persons randomized to ziprasidone versus olanzapine

• Fatal events occurring outside of a hospital setting often lack the clinical detail needed to apply specific ICD 10 codes
ZODIAC: Operational Strategies for Patient / Site Retention

• 18,154 patients were randomized
• 15,194 patients completed the 1 year follow-up (83.3%)
  – 998 withdrew consent
  – 1667 were lost to follow-up

• Strategies implemented to mitigate engagement challenges included:
  – Global study expansion, field coordinator and site relations programs, monthly site newsletters, collection of alternate contact information, NDI searches, and frequent sponsor/CRO/site interactions

CRO=Contract Research Organization; NDI=National death index
Adverse Events Occurrence in Clinical Trial Programmes

• Evaluation of adverse events observed in experimental drug arm can be compared to “placebo” arm of clinical trial
  – No difference suggests adverse events are not uniquely associated with experimental drug

• But what if data in the placebo arm are not available or it is a rare event?  What about long-term extension studies or studies that have poor patient retention?
Epidemiological Data Sources for Risk Characterisation

- Literature Review of Observational Studies
  - Patient characteristics
  - Capture of time (calendar and patient follow-up)
- Meta-analysis of Clinical Trials
  - Endpoint definitions & reporting conventions
  - Small numbers of patients & events
  - Short duration of follow-up
- Virtual Cohorts Using Pre-Existing Observational Databases
  - Sample size advantage allows stratification by patient characteristics
  - Operationalisation of endpoints
  - Methodological differences between data sources (if multiple sources are used)
Varenicline (Chantix®)

- Postmarketing spontaneous reports raised a safety concern regarding serious neuropsychiatric (NPS) adverse events
- Available data did not support the existence of a causal relationship between varenicline and serious NPS
- Results of randomized clinical trials and observational studies have recently been added to the Warnings and Precautions section of the Chantix label
Varenicline: Developed Specifically to Address Nicotine Dependence

- Varenicline binds with high affinity to $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs)
  - nAChRs are widely distributed in the brain
  - Activation of $\alpha_4\beta_2$ nAChRs in the ventral tegmental area plays a key role in mediating reinforcement- and dependence-producing effects of nicotine via dopamine release
- Varenicline is a partial agonist that
  - Has a higher $\alpha_4\beta_2$ nAChR binding affinity than nicotine and outcompetes nicotine from binding to $\alpha_4\beta_2$ nAChRs
  - Produces less dopamine release than nicotine
- These properties are thought to
  - Provide sustained, low-level dopamine release during a quit attempt
  - Inhibit the full agonist effect of nicotine during a smoking relapse
Varenicline: Possible surveillance bias

Weekly Reporting Proportion (% All Varenicline Cases Received)

Initial Received Date (Week Beginning)

- **05 Sep 2007**: Initial media reports of fatal shooting of a patient taking varenicline
- **20 Nov 2007**: FDA Early Communication
- **10 Dec 2007**: USPI update announced
- **17 Jan 2008**: 2nd USPI update
- **01 Feb 2008**: FDA press conference regarding USPI update
- **19 May 2008**: 3rd USPI update

All Suicide Related Events

Completed Suicide
## Varenicline: Observational Studies of Fatal/Non-Fatal Self Harm

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Author</th>
<th>Varenicline # Events/ Sample Size</th>
<th>Comparator # Events/ Sample Size</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limit</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>Cunningham</td>
<td>0 / 11,774</td>
<td>0 / 23,548</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Suicide</td>
<td>Thomas</td>
<td>2 / 30,352</td>
<td>6 / 78,407</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fatal Or Non Fatal Self Harm</td>
<td>Thomas</td>
<td>19 / 30,352</td>
<td>69 / 78,407</td>
<td>0.88</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Kotz</td>
<td>119 / 51,450</td>
<td>540 / 106,759</td>
<td>0.56</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Molero</td>
<td>657 / 69,757</td>
<td>NA</td>
<td>1.00</td>
<td>0.72</td>
</tr>
</tbody>
</table>

CI = confidence interval; NA = not applicable
Inter-relationship between a Clinical Trial Programme & External Patient Cohorts

Need to characterise target population according to co-morbidities, complications and safety concerns

Clinical trial programme

Observational Cohort

Findings Inform Clinical Trial Programmes
Case Study #1: Primary Care Therapy A

Subjects from Clinical Trial Programme A → Exposed Cohort

Patient data from Registry B → Trial-Criteria Subcohort*

→ Overall Comparator Cohort

Patient Characteristics of Interest

Endpoints of Interest
- Incidence Rates†

*To capture patients with similar demographic and clinical characteristics to the clinical programme under study (i.e., disease severity, age group, median/mean follow-up time, comorbidities)
†Age- and sex-standardised
Case Study #2: Specialty Care Therapy A

Subjects from Clinical Trial Programme A

Exposed Cohort

Trial-Criteria Subcohort*

Overall Comparator Cohort

Subcohort 1
Subcohort 2
Subcohort 3

Patient data from Databases B, C & D

Patient Characteristics of Interest

Endpoints of Interest
- Incidence Rates†

*To capture patients with similar demographic and clinical characteristics to the clinical programme under study (i.e., disease severity, age group, median/mean follow-up time, comorbidities)
†Age- and sex-standardised
Data Comparisons: Observed/Expected Analyses

- **Standardised Incidence Ratios (SIR)**
  - Standardised against the age & sex distribution of a comparator population
  - Interpreted like an RR or OR
    - >1.0 is increased risk, <1.0 decreased risk

- **Data Sources**
  - Electronic health records and patient registries
  - Long-standing history of safety evaluations & regulatory application
  - Sample sizes & endpoint operationalisation

- **Events of interest**
  - All-cause mortality & cardiovascular events
Standardised Incidence Ratios and 95% CIs Comparing Pfizer Drug X Subjects with Trial-Criteria Register Subcohorts of Patients Initiating their 1\textsuperscript{st}, 2\textsuperscript{nd} or 3\textsuperscript{rd} therapy within 3 External Databases

<table>
<thead>
<tr>
<th>Database</th>
<th>1\textsuperscript{st} tx</th>
<th>2\textsuperscript{nd} tx</th>
<th>3\textsuperscript{rd} tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>0.35 ± 0.13</td>
<td>0.81 ± 0.53</td>
<td>0.8 ± 0.75</td>
</tr>
<tr>
<td>C</td>
<td>0.31 ± 0.13</td>
<td>0.75 ± 0.53</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.29 ± 0.13</td>
<td>0.53 ± 0.53</td>
<td></td>
</tr>
</tbody>
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CI=confidence interval; PY=patient-years; tx=treatment
Standardised Incidence Ratios and 95% CIs Comparing Pfizer Drug X Subjects with Trial-Criteria Register Subcohorts of Patients Initiating their 1\textsuperscript{st}, 2\textsuperscript{nd} or 3\textsuperscript{rd} therapy within 3 External Databases

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<tr>
<td>B</td>
<td>0.62 ± 0.04</td>
<td>0.55 ± 0.03</td>
<td>0.39 ± 0.02</td>
</tr>
<tr>
<td>C</td>
<td>0.73 ± 0.03</td>
<td>0.4 ± 0.02</td>
<td>0.88 ± 0.05</td>
</tr>
<tr>
<td>D</td>
<td>0.84 ± 0.04</td>
<td>0.94 ± 0.03</td>
<td>1.18 ± 0.05</td>
</tr>
</tbody>
</table>

CI=confidence interval; PY=patient-years; tx=treatment

Major Adverse Cardiovascular Events

Number of events:
- Database B: 64, 31, 23
- Database C: 20, 6, 3
- Database D: 34, 17, 6

Total PY:
- Database B: 9770, 4092, 2191
- Database C: 3922, 976, 750
- Database D: 7271, 4192, 2004

1\textsuperscript{st} tx, 2\textsuperscript{nd} tx, 3\textsuperscript{rd} tx
Learnings

• What worked well
  – Common protocol
  – Common statistical plan (with formatted tables)
  – Common endpoint operationalisation
  – Face-to-face meetings

• Knowledge gained
  – Adequate operational and scientific support is critical, both internally and externally
  – Ad hoc queries happen

• Challenges
  – Pooling of data for rare events across registries
  – Methodological differences in data sources
  – Data confidentiality
  – Timelines
Conclusions

- Registries and other patient databases provide viable options for risk characterisation.

- While collaborations between databases and industry are possible, success is contingent on:
  - Timelines
  - Established protocols/statistical analysis plans
  - Methodological differences between data sources
  - Sample sizes
  - Operational and scientific support (i.e., programming & statistics)

- Additional work is needed to help address rare diseases and outcomes (i.e., pooling data sources, meta-analytic techniques, etc.)
Thank you.