Feasibility Analysis of Mortality Outcomes in the Sentinel Distributed Database

Richard Scott Swain, PhD, MPH
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Division of Epidemiology 1
U.S. Food and Drug Administration

August 28, 2017

Disclosure: This project was supported in part by an appointment to the ORISE Research Participation Program at the Center for Drug Evaluation and Research (CDER) administered by the Oak Ridge Institute for Science and Education through an agreement between the U.S. Department of Energy and CDER. The opinions in this presentation are those of the authors, and not necessarily those of the U.S. Food and Drug Administration.
Background

• Sentinel has greatly expanded FDA’s post-marketing safety surveillance and research capabilities

• While many health outcomes have been evaluated in Sentinel, mortality remains generally uncharacterized

• Assessment of available mortality data in the Sentinel Death Table will help inform FDA on the appropriateness of its use in safety studies
Objective

- To determine the feasibility of using all-cause and cause-specific mortality as outcomes for post-marketing safety studies in the Sentinel Distributed Database (SDD)
Methods

• 7 data partners (DP) contributed total and cause specific mortality from suicide from 2004 to 2012
  – Available data years varied by DP, with most DPs contributing as early as 2000 and some as recently as 2015
  – Cause of Death Table in Sentinel primarily populated from state death records

• Calculated crude rates of all-cause mortality and suicide (ICD-10-CM: X60-84, Y87.0)
  – Used insured person-time (enrollment start date to enrollment end date) as denominator

• Calculated proportional mortality from suicide

• Results stratified by DP, sex, age-group, and calendar year and compared to national estimates from CDC WONDER¹
Methods

• Sample size analysis\textsuperscript{2} for CDC 10 leading causes of death\textsuperscript{3}

\[ m = \frac{1}{k} \left( \frac{k \theta + 1}{\theta - 1} \right)^2 \left( z_{1-\alpha/2} + z_{1-\beta} \right)^2 \]

\[ n_E = \frac{mk}{kp_E + p_C} \]

\[ n_C = \frac{m}{kp_E + p_C} \]

\( m \) is the expected number of events in both groups

\( k = \frac{n_E}{n_C} \) is the ratio of experimental group to control group

\( \theta \) is the hazard ratio

\( \beta \) is Type II error, \( 1 - \beta \) is power

\( n_E \) is the number of people in the experimental group

\( n_C \) is the number of people in the control group

\( p_E \) is the probability of an event in the experimental group

\( p_C \) is the probability of an event in the control group

Assumptions:

1. Follow-up: 3 years
2. 20\% lost to follow-up per year
3. 1:1 matching
4. Average mortality rates
Results

• For study period 2004 to 2012
  – 480,389 deaths
  – 5,811 suicides
  – 67.6 million person-years of follow-up
  – Comparison to CDC WONDER

Table 1. Comparison of overall mortality and suicide rates in Sentinel vs. CDC wonder

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Mortality Rate per 100,000 person years</th>
<th>Suicide Rate per 100,000 person years</th>
<th>Proportional Mortality from Suicide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel (DP median)</td>
<td>608</td>
<td>7.5</td>
<td>1.9%</td>
</tr>
<tr>
<td>CDC WONDER</td>
<td>929</td>
<td>11.8</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
Total Deaths and Suicides by Year

Total Deaths and Suicides (2000-2015)
Death Rates by Year


- CDC WONDER
- Sentinel (select partners)
- Sentinel (all partners)
Suicide Results:
Suicide Rates and Proportional Mortality

Suicide Rates (2000-2015)
Males and Females, all Age-Groups

Suicide Rates by Data Partner (2000-2015)
Males and Females, all Age-Groups

Suicide Proportional Mortality (2000-2015)
Males and Females, all Age-Groups

Suicide Proportional Mortality by Data Partner (2000-2015)
Males and Females, all Age-Groups
Suicide Rates
Subgroup Example (Females)
Proportional Mortality Subgroup Example (Males)
### CPH Sample Size Analysis

**Table 2. Estimated Sample Size for Time to Event Analysis by Cause of Mortality and Expected Hazard Ratio**

Assumptions: Follow-up 3 years, 20% lost to follow-up per year, 1:1 matching, average mortality rates

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Sentinel Results (2004-2012)</th>
<th>Minimum Sample Size in Exposed Group for Time to Event Analysis with 80% Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Rate per 100,000py</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>479,694</td>
<td>709.2</td>
</tr>
<tr>
<td>Diseases of heart</td>
<td>196,364</td>
<td>290.3</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>125,433</td>
<td>185.4</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases</td>
<td>57,019</td>
<td>84.3</td>
</tr>
<tr>
<td>Accidents (unintentional injuries)</td>
<td>13,643</td>
<td>20.2</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>48,286</td>
<td>71.4</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>28,909</td>
<td>42.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>54,449</td>
<td>80.5</td>
</tr>
<tr>
<td>Influenza and pneumonia</td>
<td>39,842</td>
<td>58.9</td>
</tr>
<tr>
<td>Intentional self-harm (suicide)</td>
<td>5,811</td>
<td>8.6</td>
</tr>
<tr>
<td>Nephritis, nephrotic syndrome and nephrosis</td>
<td>48,803</td>
<td>72.1</td>
</tr>
</tbody>
</table>
Discussion

• Can we measure all-cause mortality?
  – Yes!
  – 53,000 deaths per year (2004-2012)

• Can we measure suicide, other causes of mortality?
  – Yes...
  – 650 suicides per year (2004-2012)
  – However, can not differentiate between immediate, contributing, and underlying causes of death
    • Possible exceptions: unintentional injuries, influenza/pneumonia, suicide
Discussion

• Rates for death and suicide were below national estimates for most data partners
  – Possibly due to younger population within SDD compared to general US
• Proportional mortality estimates for suicide: DPs were more equally split above and below national estimates
• Rates and proportional mortality were more similar to national estimates within gender/age subgroups
Strengths and Limitations

• Limitations:
  – Only examined death and cause of death among data partners populating both tables
  – Among participating DPs, most (n=5) provided cause of death data beyond 2012; majority had 2-4 year lag
  – Heterogeneity: death and suicide rates ranged from 0.2 to 3 times national estimates
  – Rare cause-specific death outcomes may have few events
  – Cause specific death outcomes other than suicide not explored in detail

• Strengths:
  – National trends of decreasing overall mortality and increasing rates and proportional mortality for suicide during the study period were reflected within DP-level data
  – High power for all-cause mortality and common causes of death
  – Follow-up options: end of enrollment or end of enrollment year
Conclusions

• Overall, all-cause mortality data in Sentinel appears promising for use as a safety outcome

• Rates and trends of completed suicide within Sentinel suggest events are well-captured

• Feasibility of Sentinel studies using cause specific mortality as an outcome will largely depend on rate of exposure (among other factors)
References

1Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2015 on CDC WONDER Online Database, released December, 2016. Data are from the Multiple Cause of Death Files, 1999-2015, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10.html on Jan 11, 2017 10:40:10 AM


Acknowledgements

Many thanks are due to Data Partners who provided data used in the analysis.

**FDA**
- Andrew Mosholder
- Lockwood Taylor
- Simone Pinheiro
- Michael Nguyen

**Sentinel**
- Tiffany Woodworth
- Candace Fuller
- Andrew Petrone
- Talia Menzin
- Nicole Haug
- Daren Toh
Questions?