Experience from US FDA Sentinel Initiative Studies

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Disclosures

• I am funded by FDA to work in the Sentinel System
Collaborating Organizations

Lead – HPHC Institute

Data & Scientific Partners

Scientific Partners

https://www.sentinelinitiative.org/collaborators
Sentinel approach to enhance validity & reduce heterogeneity

• Standardized data structure

• Robust data quality assurance process

• Pre-tested, customizable analytic tools

• Standardized analytic plan that also allows site-specific analysis
Sentinel approach to enhance validity & reduce heterogeneity

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Harmonizing multiple databases

Individual Data Partners

- Site 1
- Site 2
- Site 3
- Site 4

Data standardization

- Site 1
- Site 2
- Site 3
- Site 4

Data accessible to surveillance projects

- Surveillance projects
- Programs written against common data model

Data quality improvement feedback loop

Adapted from: http://www.hcsrn.org/asset/b9efb268-eb86-400e-8c74-2d42ac57fa4f/VDW.Infographic031511.jpg
# Sentinel Common Data Model v7.0

## Administrative Data

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Demographic</th>
<th>Dispensing</th>
<th>Encounter</th>
<th>Diagnosis</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Enrollment Start &amp; End Dates</td>
<td>Birth Date</td>
<td>Dispensing Date</td>
<td>Service Date(s)</td>
<td>Service Date(s)</td>
<td>Service Date(s)</td>
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<tr>
<td>Drug Coverage</td>
<td>Sex</td>
<td>National Drug Code (NDC)</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
</tr>
<tr>
<td>Medical Coverage</td>
<td>Zip Code</td>
<td>Days Supply</td>
<td>Encounter Type and Provider</td>
<td>Encounter Type and Provider</td>
<td>Encounter Type and Provider</td>
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<td>Medical Record Availability</td>
<td>Etc.</td>
<td>Amount Dispensed</td>
<td>Facility</td>
<td>Diagnosis Code &amp; Type</td>
<td>Procedure Code &amp; Type</td>
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## Clinical Data

<table>
<thead>
<tr>
<th>Lab Result</th>
<th>Vital Signs</th>
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<tr>
<td>Patient ID</td>
<td>Patient ID</td>
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<tr>
<td>Result &amp; Specimen Collection Dates</td>
<td>Measurement Date &amp; Time</td>
</tr>
<tr>
<td>Test Type, Immediacy &amp; Location</td>
<td>Height &amp; Weight</td>
</tr>
<tr>
<td>Logical Observation Identifiers Names and Codes (LOINC®)</td>
<td>Diastolic &amp; Systolic BP</td>
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<td>Tobacco Use &amp; Type</td>
<td>Etc.</td>
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## Registry Data

<table>
<thead>
<tr>
<th>Death</th>
<th>Cause of Death</th>
<th>State Vaccine</th>
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<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Death Date</td>
<td>Cause of Death</td>
<td>Vaccination Date</td>
</tr>
<tr>
<td>Source</td>
<td>Source</td>
<td>Admission Date</td>
</tr>
<tr>
<td>Confidence</td>
<td>Confidence</td>
<td>Vaccine Code &amp; Type</td>
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<tr>
<td>Etc.</td>
<td>Etc.</td>
<td>Provider</td>
</tr>
<tr>
<td></td>
<td>Etc.</td>
<td>Etc.</td>
</tr>
</tbody>
</table>

## Inpatient Data

### Inpatient Pharmacy

<table>
<thead>
<tr>
<th>Inpatient Pharmacy</th>
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<tbody>
<tr>
<td>Patient ID</td>
</tr>
<tr>
<td>Administration Date &amp; Time</td>
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<tr>
<td>Encounter ID</td>
</tr>
<tr>
<td>National Drug Code (NDC)</td>
</tr>
<tr>
<td>Route</td>
</tr>
<tr>
<td>Dose</td>
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<td>Blood Type</td>
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</table>

### Inpatient Transfusion

<table>
<thead>
<tr>
<th>Inpatient Transfusion</th>
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<tbody>
<tr>
<td>Patient ID</td>
</tr>
<tr>
<td>Administration Start &amp; End Date &amp; Time</td>
</tr>
<tr>
<td>Encounter ID</td>
</tr>
<tr>
<td>Transfusion Administration ID</td>
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<tr>
<td>Transfusion Product Code</td>
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<td>Etc.</td>
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## Mother-Infant Linkage Data

<table>
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<td>Mother ID</td>
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<td>Mother Birth Date</td>
</tr>
<tr>
<td>Encounter ID &amp; Type</td>
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<tr>
<td>Admission &amp; Discharge Date</td>
</tr>
<tr>
<td>Child ID</td>
</tr>
<tr>
<td>Child Birth Date</td>
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<tr>
<td>Mother-Infant Match Method</td>
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<td>Etc.</td>
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</table>
Sentinel approach to enhance validity & reduce heterogeneity

- Standardized data structure
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- Pre-tested, customizable analytic tools
- Standardized analytic plan that also allows site-specific analysis
Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

Sentinel Data Quality Review and Characterization Process

1. Preparation
   Sentinel Operations Center prepares quality review and characterization package for new ETL

2. Transformation
   Data Partner transforms source data into the Sentinel Common Data Model

3. Distribution
   Sentinel Operations Center distributes quality assurance package to Data Partners

4. Model Compliance
   Data Partner runs quality review and characterization package completing the following:
   • Level 1 checks
   • Level 2 checks
   Quality review and characterization package outputs list of errors or anomalies (flags) identified during data checks
   Data Partner resolves these flags and sends a detailed report to the Sentinel Operations Center

5. Review & Characterization
   Sentinel Operations Center receives output from Data Partner and reviews
   • Level 2 checks
   • Level 3 checks
   • Level 4 checks
   Sentinel Operations Center evaluates any additional flags and creates issue report for Data Partner to address

6. Completion
   Data Partner investigates issues identified in report generated by the Sentinel Operations Center and resolves remaining flags

7. Approval
   Sentinel Operations Center Quality Assurance Manager approves ETL for use in queries

* On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL

- Consistent with FDA’s best practices
- Data not used in any analysis unless passing QA
- **1,400+** checks per site per refresh
Sentinel approach to enhance validity & reduce heterogeneity

• Standardized data structure

• Robust data quality assurance process

• **Pre-tested, customizable analytic tools**

• Standardized analytic plan that also allows site-specific analysis
Analytic framework (one-off)

1. Identify health plan members aged ≥18 years in year 2001-2014
2. Restrict to patients with a dispensing of oral ACEIs or ß-blockers
3. Restrict to patients with ≥183 days health plan enrollment
4. Restrict to patients with no diagnosis of angioedema in prior 183 days
5. Follow patients from index date until diagnosis of angioedema or end of treatment
Analytic framework (re-usable)

1. Identify health plan members aged ≥18 years in year 2001-2014
2. Restrict to patients with a dispensing of oral ACEIs or ß-blockers
3. Restrict to patients with ≥183 days health plan enrollment
4. Restrict to patients with no diagnosis of angioedema in prior 183 days
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Analytic framework (re-usable)

1. Identify health plan members aged ≥18 years in year 2001-2014
2. Restrict to patients with a dispensing of oral ACEIs or β-blockers
3. Restrict to patients with ≥183 days health plan enrollment
4. Restrict to patients with no diagnosis of angioedema in prior 183 days
5. Follow patients from index date until diagnosis of angioedema or end of treatment
Propensity score analysis in Sentinel

1. Identify exposure and comparator cohorts
2. Extract covariate information
3. Estimate an exposure propensity score
4. Match/stratify exposed & comparator patients on PS
5. Generate effect estimates and create report

Cohort Identification and Descriptive Analysis Tool

Propensity Score Analysis Tool
Propensity score analysis in Sentinel

1. **Identify exposure and comparator cohorts**
   - Female
   - Age 25
   - Diagnosis History
   - Drug History

2. **Extract covariate information**
   - Performs at Data Partner sites

3. **Estimate an exposure propensity score**
   - Propensity Score
   - Performs at Sentinel Operation Center

4. **Match/stratify exposed & comparator patients on PS**
   - Generate effect estimates and create report
Sentinel approach to enhance validity & reduce heterogeneity

- Standardized data structure
- Robust data quality assurance process
- Pre-tested, customizable analytic tools
- **Standardized analytic plan that also allows site-specific analysis**
1. User creates and submits query
2. Data Partners retrieve query
3. Data Partners review and run query against their local data
4. Data Partners review results
5. Data Partners return results via secure network
6. Results are aggregated and reported
Additional analytic capabilities

• Allow high-dimensional propensity scores
  – Database-specific covariate adjustment

• Allow pre-specify stratified or subgroup analysis
  – By Data Partner
  – By patient characteristic (e.g., age group, sex)

• Most analyses can be done with summary-level information
  – Risk-set based approaches (mathematically equivalent to pooled individual-level analysis)
Example 1 – Anti-hypertensive drugs and angioedema

<table>
<thead>
<tr>
<th>Drug</th>
<th>Site-adjusted</th>
<th>PS-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>2.77 (2.57, 2.98)</td>
<td>3.04 (2.81, 3.27)</td>
</tr>
<tr>
<td>ARBs</td>
<td>1.11 (0.97, 1.28)</td>
<td>1.16 (1.00, 1.34)</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>2.75 (1.30, 5.81)</td>
<td>2.85 (1.34, 6.04)</td>
</tr>
</tbody>
</table>

Reference group: beta-blockers
Example 1 – Anti-hypertensive drugs and angioedema

<table>
<thead>
<tr>
<th>Site</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.31 (0.43, 4.02)</td>
</tr>
<tr>
<td>2</td>
<td>4.13 (3.04, 5.59)</td>
</tr>
<tr>
<td>3</td>
<td>4.48 (3.17, 6.32)</td>
</tr>
<tr>
<td>4</td>
<td>2.29 (1.54, 3.39)</td>
</tr>
<tr>
<td>5</td>
<td>2.97 (1.95, 4.52)</td>
</tr>
<tr>
<td>6</td>
<td>1.15 (0.56, 2.33)</td>
</tr>
<tr>
<td>7</td>
<td>2.02 (0.86, 4.73)</td>
</tr>
<tr>
<td>8</td>
<td>4.04 (1.45, 11.29)</td>
</tr>
<tr>
<td>9</td>
<td>3.33 (2.16, 5.13)</td>
</tr>
<tr>
<td>10</td>
<td>2.59 (1.27, 5.30)</td>
</tr>
<tr>
<td>11</td>
<td>3.36 (2.85, 3.97)</td>
</tr>
<tr>
<td>12</td>
<td>2.84 (2.47, 3.27)</td>
</tr>
<tr>
<td>13</td>
<td>2.63 (1.76, 3.94)</td>
</tr>
<tr>
<td>14</td>
<td>3.85 (2.28, 6.50)</td>
</tr>
<tr>
<td>15</td>
<td>3.27 (2.14, 5.00)</td>
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<tr>
<td>16</td>
<td>3.78 (2.39, 5.99)</td>
</tr>
<tr>
<td>17</td>
<td>2.35 (1.90, 2.90)</td>
</tr>
</tbody>
</table>

ACEIs vs. beta-blockers

P-value for test for homogeneity: 0.01

### Example 2 – Glyburide/glipizide vs. severe hypoglycemia

*Zhou et al, Epidemiology 2017;28(6):838-846*

<table>
<thead>
<tr>
<th>Exposure</th>
<th>New Users&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Person-Years at Risk</th>
<th>Serious Hypoglycemia Events</th>
<th>Incidence Rate per 1000 Person-Years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from 13 data partners</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmatched&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>198,550</td>
<td>89,719</td>
<td>1,685</td>
<td>19</td>
<td>1.11 (1.05, 1.18)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>379,507</td>
<td>244,094</td>
<td>5,406</td>
<td>22</td>
<td>—</td>
</tr>
<tr>
<td>Predefined covariates—unconditional model&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>173,655</td>
<td>83,108</td>
<td>1,633</td>
<td>20</td>
<td>1.35 (1.26, 1.45)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>173,656</td>
<td>99,834</td>
<td>1,393</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Predefined covariates—conditional model&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Glyburide</td>
<td>173,655</td>
<td>38,986</td>
<td>1,064</td>
<td>27</td>
<td>1.36 (1.24, 1.49)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>173,656</td>
<td>38,986</td>
<td>784</td>
<td>20</td>
<td>—</td>
</tr>
</tbody>
</table>
Example 2 – Glyburide/glipizide vs. severe hypoglycemia

### TABLE 3. Incidence Rates and Hazard Ratios of Emergency Department Visits and Hospital Admissions for Hypoglycemia

<table>
<thead>
<tr>
<th>Exposure</th>
<th>New Users</th>
<th>Person-Years at Risk</th>
<th>Serious Hypoglycemia Events</th>
<th>Incidence Rate per 1000 Person-Years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmatched</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>139,113</td>
<td>58,075</td>
<td>905</td>
<td>16</td>
<td>1.26 (1.16, 1.38)</td>
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<tr>
<td>Glipizide</td>
<td>181,911</td>
<td>94,941</td>
<td>1,079</td>
<td>11</td>
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<td>Predefined covariates—unconditional model</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Glyburide</td>
<td>120,334</td>
<td>53,366</td>
<td>859</td>
<td>16</td>
<td>1.41 (1.27, 1.56)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>120,335</td>
<td>61,552</td>
<td>666</td>
<td>11</td>
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</tr>
<tr>
<td>Predefined covariates—conditional model</td>
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<td></td>
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<tr>
<td>Glyburide</td>
<td>120,334</td>
<td>24,708</td>
<td>568</td>
<td>23</td>
<td>1.42 (1.25, 1.62)</td>
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<td>Glipizide</td>
<td>120,335</td>
<td>24,708</td>
<td>399</td>
<td>16</td>
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<td>hdPS—unconditional model</td>
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<tr>
<td>Glyburide</td>
<td>116,930</td>
<td>52,816</td>
<td>870</td>
<td>17</td>
<td>1.50 (1.36, 1.66)</td>
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<tr>
<td>Glipizide</td>
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<td>62,526</td>
<td>644</td>
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<td>hdPS—conditional model</td>
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<tr>
<td>Glyburide</td>
<td>116,930</td>
<td>24,494</td>
<td>581</td>
<td>24</td>
<td>1.49 (1.31, 1.70)</td>
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<tr>
<td>Glipizide</td>
<td>116,931</td>
<td>24,498</td>
<td>389</td>
<td>16</td>
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</tr>
</tbody>
</table>

Data from five data partners in which the hdPS model converged and completed without errors.

---

### Example 2 – Glyburide/glipizide vs. severe hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Data partner 1</td>
<td>1.31 (1.13-1.52)</td>
<td>1.47 (1.24, 1.75)</td>
<td>1.47 (1.18, 1.83)</td>
<td>1.58 (1.33, 1.85)</td>
<td>1.60 (1.29, 2.00)</td>
<td>1.50 (1.26, 1.78)</td>
<td>1.42 (1.14, 1.76)</td>
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<tr>
<td>Data partner 2</td>
<td>1.48 (1.26, 1.74)</td>
<td>1.76 (1.46, 2.12)</td>
<td>1.71 (1.35, 2.18)</td>
<td>1.71 (1.43, 2.06)</td>
<td>1.61 (1.27, 2.04)</td>
<td>1.79 (1.48, 2.16)</td>
<td>1.77 (1.39, 2.26)</td>
</tr>
<tr>
<td>Data partner 3</td>
<td>1.18 (0.72, 1.65)</td>
<td>1.59 (0.84, 3.01)</td>
<td>1.67 (0.73, 3.81)</td>
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<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Data partner 4</td>
<td>1.57 (0.86, 2.86)</td>
<td>1.53 (0.75, 3.12)</td>
<td>2.60 (0.03, 7.29)</td>
<td>1.87 (0.85, 4.08)</td>
<td>1.80 (0.60, 5.37)</td>
<td>2.00 (0.92, 4.34)</td>
<td>2.40 (0.85, 6.81)</td>
</tr>
<tr>
<td>Data partner 5</td>
<td>1.61 (0.80, 3.23)</td>
<td>1.33 (0.54, 3.27)</td>
<td>1.75 (0.51, 5.98)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Data partner 6</strong></td>
<td><strong>17.72 (2.04, 153.9)</strong></td>
<td><strong>6.00 (0.75, 58.07)</strong></td>
<td><strong>72*13 (0.00...)</strong></td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Data partner 7</td>
<td>1.09 (0.54, 2.20)</td>
<td>1.41 (0.59, 2.88)</td>
<td>0.71 (0.23, 2.25)</td>
<td>1.19 (0.43, 3.27)</td>
<td>1.25 (0.34, 4.65)</td>
<td>1.19 (0.43, 3.27)</td>
<td>1.50 (0.42, 5.32)</td>
</tr>
<tr>
<td>Data partner 8</td>
<td>1.32 (1.19, 1.47)</td>
<td>1.38 (1.23, 1.56)</td>
<td>1.41 (1.21, 1.64)</td>
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<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Data partner 9</td>
<td>0.44 (0.66, 3.23)</td>
<td>1.03 (0.06, 16.51)</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Data partner 10</td>
<td>3.33 (1.27, 8.72)</td>
<td>2.30 (0.53, 9.91)</td>
<td>4.00 (0.45, 35.79)</td>
<td>--</td>
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<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Data partner 11</strong></td>
<td><strong>0.55 (0.47, 0.65)</strong></td>
<td><strong>0.96 (0.77, 1.19)</strong></td>
<td><strong>0.85 (0.63, 1.13)</strong></td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Data partner 12</td>
<td>3.52 (1.26, 9.68)</td>
<td>2.90 (0.51, 16.34)</td>
<td>1.00 (0.14, 7.10)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Data partner 13</td>
<td>1.03 (0.88, 1.21)</td>
<td>1.10 (0.92, 1.31)</td>
<td>1.16 (0.93, 1.45)</td>
<td>1.24 (1.04, 1.49)</td>
<td>1.29 (1.04, 1.61)</td>
<td>1.24 (1.04, 1.49)</td>
<td>1.29 (1.04, 1.61)</td>
</tr>
</tbody>
</table>

hdPS = High-dimensional propensity score, CI = Confidence interval.

* Hazard ratios comparing glyburide versus glipizide.

* Please note, one data partner removed a small number of users that moved to administrative services only plans. Information from these users is included in Tables 1 and 2, but removed from subsequent tables.

* The conditional models were stratified by the matched pair.

* The unconditional models were not stratified by the matched pair.
Sentinel approach to enhance validity & reduce heterogeneity

• Standardized data structure

• Robust data quality assurance process

• Pre-tested, customizable analytic tools

• Standardized analytic plan that also allows site-specific analysis
Sentinel approach to enhance validity & reduce heterogeneity

• Minimize variations in data quality, design, and analysis

• Any observed differences in results across sites would more likely indicate real treatment effect heterogeneity
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