Signal Detection using TreeScan with Drug Classes: Pilot Projects in Sentinel

Judith C. Maro\textsuperscript{1}, Michael D. Nguyen\textsuperscript{2}, Rima Izem\textsuperscript{2}, Ya-Hui Hsueh\textsuperscript{2}, Inna Dashevsky\textsuperscript{1}, Austin Cosgrove\textsuperscript{1}, S. Christopher Jones\textsuperscript{2}, Jacqueline M. Major\textsuperscript{2}, Esther H. Zhou\textsuperscript{2}, Elande Baro\textsuperscript{2}, Joshua J. Gagne\textsuperscript{3}, Shirley V. Wang\textsuperscript{3} and Martin Kulldorff\textsuperscript{3}

1. Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, MA;
2. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD;
3. Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
Disclosures

- The authors have the following conflicts of interest to disclose:
  - JJG has received salary support from grants from Eli Lilly and Company and Novartis Pharmaceuticals Corporation to the Brigham and Women’s Hospital and is a consultant to Aetion, Inc and Optum, Inc. all for unrelated work.
  - SVW is a consultant to Aetion, Inc.

- This work was supported by the U.S. Food and Drug Administration (FDA) through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I

- This presentation reflects the views of the authors and not necessarily those of the U.S. FDA.
Tree-Based Scan Statistics are Enabled by:

- A signal detection / data-mining method
- Scans electronic health outcome data that are grouped into hierarchical tree structures
- Automatically adjusts for multiple hypothesis testing

http://www.treescan.org
Multi-Level Clinical Classification System Tree

- Diseases of the Nerve and Sense Organs
  - Central Nervous System Infection
  - Hereditary and degenerative nervous system condition
  - Paralysis

- Epilepsy
- Convulsions

- Convulsions
  - Febrile convulsions NO ICD-9-CM 780.31
  - Complex febrile convulsions ICD-9-CM 780.32
  - Post traumatic seizures ICD-9-CM 780.33
  - Other convulsions ICD-9-CM 780.39

- Epilepsy; convulsions
Data Source

- 3 Data Partners in Sentinel Distributed Database
  - Represents ~35% of the Overall Sentinel Distributed Database
  - Data from 2000 to Latest Available (between 2016-2017)
Three Medical Product Study Classes (Test Cases)

- Long-Acting Reversible Contraceptives
  - Small Sample Size
  - Medically-attended procedures present as point exposures

- Statins
  - Large Sample Size
  - Established Safety Record

- Selected Antibiotics
  - Very Large Sample Size
  - Therapeutic administered in an urgent treatment situation
Universal Self-Controlled Study Design Diagram

- No Study Drug in [-183,-1]
- Study-Specific Exclusions with varying Time Periods
- No Prior Outcomes in the 4th Level of the MLCCS Tree in 183 days
- TreeScan Observation Window [1,56]
- New Study Drug Use
- ED or IP Outcome
- Pre-Exposure Enrollment Requirements [-183,0]
- Post-Exposure Enrollment Requirements [1,56]
- Continuous Enrollment Requirements (w/45-d gaps)

Query Start Date

Query End Date
Conditional Tree-Temporal Scan Statistic

Under the null hypothesis, there is no unusual clustering of events within any node or clinically-related group during any time interval.

Under the alternative hypothesis, there is at least one node or clinically-related group of the tree for which there is a temporal cluster of events during some time interval.
Results
Intrauterine Device (IUD) Cohort Attrition

- IUD insertions during the query period: 775,037
  - Incident IUD insertions: 701,704
    - Incident IUD insertions with enrollment: 295,726
      - Incident IUD insertions after exclusions: 217,339
        - Incident outcomes: 19,396

- Non-incident IUD insertions: 73,333 (10%)
- Incident IUD insertions without required enrollment: 355,812 (50%)
- Incident IUD insertions with exclusions: 78,387 (27%)
<table>
<thead>
<tr>
<th>Node Name</th>
<th>Node ID</th>
<th>Node Outcomes</th>
<th>Node Outcomes in Risk Window</th>
<th>RW Start</th>
<th>RW End</th>
<th>Relative Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital pain and other symptoms</td>
<td>10030901</td>
<td>612</td>
<td>115</td>
<td>1</td>
<td>4</td>
<td>2.74</td>
<td>0.0001</td>
</tr>
<tr>
<td>….Female genital symptoms NOS</td>
<td>6259</td>
<td>576</td>
<td>112</td>
<td>1</td>
<td>4</td>
<td>2.85</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other complications of internal prosthetic device; implant; and graft</td>
<td>16100103</td>
<td>114</td>
<td>30</td>
<td>1</td>
<td>4</td>
<td>4.09</td>
<td>0.0003</td>
</tr>
<tr>
<td>….Complication NEC due to GU device</td>
<td>99676</td>
<td>106</td>
<td>29</td>
<td>1</td>
<td>4</td>
<td>4.31</td>
<td>0.0002</td>
</tr>
<tr>
<td>Other specified non-inflammatory disorders of vagina</td>
<td>6238</td>
<td>254</td>
<td>200</td>
<td>2</td>
<td>29</td>
<td>3.21</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

These “alerts” are not unexpected and reflect routine but rare complications of IUD insertions.
Simvastatin Cohort Attrition

Exposed Cohort

Exposures during the query period 60,782,432

Incident exposures 6,023,613

Incident exposures with enrollment 1,710,446

Incident exposures after exclusions 1,695,892

Incident outcomes 405,468

Analytic Cohort

Non-incident exposures 54,758,819 (90%)

Incident exposures without required enrollment 4,313,167 (72%)

Incident exposures with exclusions 14,554 (0.9%)
<table>
<thead>
<tr>
<th>Node Name</th>
<th>Node ID</th>
<th>Node Outcomes</th>
<th>Node Outcomes in Risk Window</th>
<th>RW Start</th>
<th>RW End</th>
<th>Relative Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina (intermediate coronary syndrome)</td>
<td>07020402</td>
<td>2269</td>
<td>523</td>
<td>1</td>
<td>7</td>
<td>1.68</td>
<td>0.0001</td>
</tr>
<tr>
<td>...Intermediate Coronary Syndrome</td>
<td>4111</td>
<td>2269</td>
<td>523</td>
<td>1</td>
<td>7</td>
<td>1.68</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>07020401</td>
<td>1408</td>
<td>377</td>
<td>1</td>
<td>8</td>
<td>1.77</td>
<td>0.0001</td>
</tr>
<tr>
<td>....Angina Pectoris NEC &amp; NOS</td>
<td>4139</td>
<td>1353</td>
<td>360</td>
<td>1</td>
<td>8</td>
<td>1.76</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardiac arrest and ventricular fibrillation</td>
<td>07021000</td>
<td>459</td>
<td>160</td>
<td>44</td>
<td>56</td>
<td>1.95</td>
<td>0.0006</td>
</tr>
<tr>
<td>...Cardiac Arrest</td>
<td>4275</td>
<td>307</td>
<td>106</td>
<td>47</td>
<td>56</td>
<td>2.61</td>
<td>0.0001</td>
</tr>
<tr>
<td>Disorders of lipid metabolism</td>
<td>03060000</td>
<td>7449</td>
<td>2269</td>
<td>1</td>
<td>13</td>
<td>1.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other forms of chronic heart disease</td>
<td>07020405</td>
<td>5447</td>
<td>1676</td>
<td>1</td>
<td>13</td>
<td>1.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemorrhage or hematoma complicating a procedure</td>
<td>16100205</td>
<td>990</td>
<td>227</td>
<td>1</td>
<td>7</td>
<td>1.67</td>
<td>0.0002</td>
</tr>
<tr>
<td>...Hematoma Complicating a Procedure</td>
<td>99812</td>
<td>451</td>
<td>113</td>
<td>1</td>
<td>6</td>
<td>2.25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Conditions associated with dizziness or vertigo</td>
<td>06080200</td>
<td>4633</td>
<td>628</td>
<td>1</td>
<td>5</td>
<td>1.3</td>
<td>0.0011</td>
</tr>
<tr>
<td>...Dizziness &amp; Giddiness</td>
<td>7804</td>
<td>4210</td>
<td>578</td>
<td>1</td>
<td>5</td>
<td>1.32</td>
<td>0.0006</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>08060100</td>
<td>3063</td>
<td>804</td>
<td>42</td>
<td>54</td>
<td>1.29</td>
<td>0.0031</td>
</tr>
<tr>
<td>Surgical Complication-Peripheral Vascular</td>
<td>9972</td>
<td>121</td>
<td>40</td>
<td>1</td>
<td>6</td>
<td>3.32</td>
<td>0.0099</td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td>07020404</td>
<td>6247</td>
<td>1243</td>
<td>1</td>
<td>8</td>
<td>1.2</td>
<td>0.0100</td>
</tr>
<tr>
<td>Lower extremity aneurysm</td>
<td>4423</td>
<td>82</td>
<td>28</td>
<td>1</td>
<td>5</td>
<td>4.29</td>
<td>0.0100</td>
</tr>
<tr>
<td>Name</td>
<td>Exposure Cohort</td>
<td>Analytic Dataset</td>
<td>Alerts at 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>7,500,871 episodes</td>
<td>1,412,160 events</td>
<td>174 alerts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3,706,774 episodes</td>
<td>1,206,543 events</td>
<td>209 alerts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1,506,530 episodes</td>
<td>638,717 events</td>
<td>72 alerts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Overwhelmed by signs and symptoms followed by individuals with profiles for acute organ failure, septic shock, and other acute traumatic events.
Limitations

- **Self Controlled Design:**
  - Depends on onset times in the data model
  - May capture alerts due to signs and symptoms related to drug indications
  - Cannot distinguish sustained elevated risk of outcome
  - Is vulnerable to time-varying confounding

- **Analytic Limitations:**
  - Acute outcome events only with fixed follow-up
Summary

- We empirically tested tree-temporal scan statistics in 3 different drug classes.
- Self-controlled TreeScan methods performed as expected:
  - Best when applied to stable patients (eg, contraceptives, vaccines)
  - Moderate performance for statins; Better performance possible with more careful exclusion criteria for recently hospitalized / unstable patients
  - Poor performance for acutely ill, unstable patients
- New propensity score based TreeScan may better account for these conditions (more unstable patient populations)
  - Next Up: Shirley Wang presents “Data mining for adverse drug events with a propensity score matched tree-based scan statistic”
Additional Acknowledgements

Sentinel Operations Center
- Meighan Rogers-Driscoll
- David Cole
- Ella Pestine

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

Food & Drug Administration (FDA)
- Rita Ouellet-Hellstrom