Adverse Event Signal Detection
Overall Comparisons, Future Projections and False Discoveries

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Example

• Phase 3 trial:
  449 AEs observed, $N_A$ and $N_B$ about 500

• 50 AEs have $z$-values > 1.96
  Under the null, expect 11 AEs ($= .025 \times 449$)
Question of Interest

• How many more subjects would experience AEs if trial period is extended?
Outline

• **Step 1**: graphically compare z scores with null distn

• **Step 2**: flag AEs by controlling FDR

• **Step 3**: for each AE, project number of subjects with a given AE into the future, using ALL AE data

• **Step 4**: Re-flag AEs by controlling FDR

• Pay attention to new AEs flagged. Informal inference.
Example: Graphical Comparison

- Large data set density
- Standard normal density

Shift to the right.
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FDR: q-values (Storey’s FDR)

- FDR: false discovery rate
- q-value is to FDR what p-value is to PCER
- Interpretation: Suppose for AE i q-value = 0.01. Then we expect 1% of AEs with p-value < 0.01 to be false positives

Example data set: 29/449 AEs (6.5%) had q-values < 0.025
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**Projections: New Idea**

**Group A:**

\[ \text{# subjects with AE at t2} = \text{# at t1} + \text{Project # in (t2 – t1) under null} \]

\[ + \text{Project # in (t2 – t1) undernonnull} \]

Take weighted average

**New Approach**

\[ \text{# at t2} = \text{# at t1} + w \times \text{# in (t2-t1) under null} \]

\[ + (1-w) \times \text{# in (t2-t1) under nonnull} \]

\[ w = P(\text{null true for AE i | z_i}) \]

(Efron’s empirical Bayes idea, JASA 2004)
# of Subj with AE $i$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T1</th>
<th>T2 = T1 + delta</th>
<th>Under H$_0$</th>
<th>Under H$_1$</th>
<th>Weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20</td>
<td></td>
<td>33</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td></td>
<td>23</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>A - B</td>
<td>10</td>
<td></td>
<td>10</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>$w_i = 0.7$</td>
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</tbody>
</table>

No. with event under H$_0$ or H$_1$ is modeled given observed data

$w_i = P$(null true for AE $i$ | $z_i$)
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Example data set: 24 mth and 30 mth Z-values

- 29 significant AEs at the end of study
- Additional 2 flagged by projection
Reality Check: Projecting from 20 to 24 Months

- Assumed survival distribution is exponential.

- Did not account for subjects who were censored between Months 20 and 24.
Reality Check: Projecting from 20 to 24 Months

Comparison of Z-scores Based on Observed Data and Projected Data

Correlation = 0.9894
Recap: Key Elements

• Compare observed data with N(0,1)

• Weight each AE to reflect the null and non-null simultaneously (empirical Bayes)

• Project # with AEs in the future: gain information

• q-values: apply to observed time and future time. Pay attention to additional AEs flagged
Pros and Cons of Method

• Pros
  - Helps with: “what would happen if trial period extended?”
  - Projection for AE i based on ALL AE data

• Cons
  - Assumes all subjects risk-free at observed time are at risk until future time
  - Doesn’t work with expected or acute events

• Additional details in “Adverse Event Signal Detection: Overall Comparisons, Future Projections and False Discoveries” (J Ma, J Ganju, J Huang). Submitted for publication.