Likelihood Ratio-Based Tests for Longitudinal Safety Data

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Ram Tiwari and Lan Huang
Office of Biostatistics, CDER, FDA
Disclaimer

The views expressed by the speakers of this talk are their own and do not necessarily represent those of FDA.
Useful references


2. Lan Huang, Jyoti Zalkikar, Ram Tiwari. Likelihood ratio tests for longitudinal drug safety data. Statistics in Medicine, 33(14), 2408-2424, 2014

Outline

• Basic LRT method for large post-market safety database
• OB in-house tool development and illustration
• Longitudinal LRT method for data with exposure information
• Discussion
Background

• Large databases: AERS, Vigibase, MAUDE
• Data mining methods (frequentist, Bayesian, OMOP/IMEDS)
• Objective of the safety exploration
  – Signal detection in large safety database
  – Clinical trials database
  – Passive/active
# Safety Data-Matrix for AERS Database

## Drugs

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>...</th>
<th>j</th>
<th>...</th>
<th>J</th>
<th>Row total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n_{11})</td>
<td>...</td>
<td>(n_{1j})</td>
<td>...</td>
<td>(n_{1J})</td>
<td>(n_{1.})</td>
</tr>
<tr>
<td>2</td>
<td>(n_{21})</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>(n_{2J})</td>
<td>(n_{2.})</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>i</td>
<td>...</td>
<td>...</td>
<td>(n_{ij})</td>
<td>...</td>
<td>(n_{ij})</td>
<td>(n_{i.})</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>I</td>
<td>(n_{I1})</td>
<td>...</td>
<td>(n_{ij})</td>
<td>...</td>
<td>(n_{Ij})</td>
<td>...</td>
</tr>
<tr>
<td>Col. total</td>
<td>(n_{.1})</td>
<td>...</td>
<td>(n_{.J})</td>
<td>...</td>
<td>(n_{.J})</td>
<td>(n_{..})</td>
</tr>
</tbody>
</table>

## AEs

- \(n_{ij}\): Frequency of AE occurrence for drug \(i\) and AE \(j\).
• Fix a drug, say Drug j, and construct a 2X2 table for each AE: If there are, say, 16,000 AEs, then there are 16,000 such 2x2 tables
• Most of the frequentist’s methods and some Bayesian methods work with 2X2 tables

<table>
<thead>
<tr>
<th></th>
<th>Drugj</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_{ij}$</td>
<td>Subtracted</td>
<td>$n_i.$</td>
</tr>
<tr>
<td>Other AEs</td>
<td>Subtracted</td>
<td>Subtracted</td>
</tr>
<tr>
<td>$n_j.$</td>
<td>Subtracted</td>
<td>$n_{..}$</td>
</tr>
</tbody>
</table>
Statistical model and hypothesis

\[ n_{ij} \sim \text{Pois}(n_{i.} p_i) \]
\[ n_{.j} - n_{ij} \sim \text{Pois}((n_{..} - n_{i.}) \times q_i) \]

\[ H_0 : p_i = q_i = p^* \quad \text{for all AEs, i} \]

\[ H_a : p_i > q_i \quad \text{for all at least one AE, i} \]

\[ \text{RR} = \frac{p}{q}, \text{AE i vs. other AEs} \]

\[ LR = \max L_a / \max L_0 \]
Likelihood Ratio Test (LRT) statistic

\[ LR_{ij} = \frac{L_a(\hat{p}, \hat{q})}{L_0(\hat{p}^*)} = \left[ \left( \frac{n_{ij}}{n_i.} \right)^{n_{ij}} \left( \frac{n_{.j} - n_{ij}}{n_{..} - n_i.} \right)^{n_{.j} - n_{ij}} \right] \]

- Test Statistic is MaxLR=max of LR_{ij} (i=1 to I) over i=1,…,I AEs.
- LogLR and MaxLogLR can be used for faster computation
Re-parametrization and adjustment

\[ LR_{ij} = \left( \frac{n_{ij}}{n_i \times \frac{n_j}{n_..}} \right)^{n_{.j}-n_{ij}} \left( \frac{n_{.j}-n_{ij}}{(n_..-n_{i.}) \times \frac{n_j}{n_..}} \right)^{n_{.j}-n_{ij}} = \left( \frac{n_{ij}}{E_{ij}} \right)^{n_{ij}} \left( \frac{n_{.j}-n_{ij}}{n_{.j}-E_{ij}} \right)^{n_{.j}-n_{ij}} \]

\[ E_{ij} = \frac{n_i \times n_j}{n_..} = n_i \times \frac{n_j}{n_..} \]

To adjust for a covariate (such as age or gender)(stratified analysis), we simply calculate the age-adjusted or gender adjusted expected cases. We first calculate the \( E_{ijk}, k=1,2 \) (by gender), then we combine them together.

\[ E_{ij} = \sum_k E_{ijk}^k = \sum_k \left[ n_i^k \times \frac{n_j^k}{n_..^k} \right] \]
Theory behind the multinomial simulation for the null data

Assume that the marginal totals $n_1., \ldots, n_l.$, are fixed. Under H0, assume that $n_{1j}, \ldots, n_{lj}$ are ind distributed as

\[
n_{1j} \sim \text{Poisson}(n_1.p).
\]

\[
\ldots
\]

\[
n_{lj} \sim \text{Poisson}(n_1.p), \ p > 0, \text{unknown}.
\]

Then,

\[
(n_{1j}, \ldots, n_{lj}) \mid n_{.j} \sim \text{mult}(n_{.j}, \left(\frac{n_1.}{n_{..}}, \ldots, \frac{n_l.}{n_{..}}\right)).
\]
Hypothesis testing

• The distribution of MaxLR under H0 is not analytically tractable, we use Monte Carlo method to obtain the empirical dist.

• Cases can be generated using multinomial distribution (n.j, (n1./n..), (n2./n..), ...., (nI./n..)) assuming homogeneous reporting rate.
P-value calculation

• Calculate MaxLR from observed data (one)

• Calculate MaxLRs from the 9,999 simulated null data.

• Threshold at alpha=0.05 is 95 percentile of the 10,000 (=1+9999) MaxLRs.

• Reject H0 if obs MaxLR > threshold.

• Compare the observed MLR and the ones from simulation \(\rightarrow\) p-value = \(P(MLR > obs \text{ MaxLR}) = \text{Max } \#\text{ of times simulated MaxLR} > obs \text{ MaxLR} / 10000\).

• Gatekeeping step-down process (1\text{st}, 2\text{nd}, 3\text{rd}, …)
LRT process for a drug (jth column)

One observed data

LR1j
LR2j
LR3j
.....

LR1*j (maxLR_obs)
LR2*j
LR3*j
.....

Rank of the obs among 1+9999

maxLR_H0_1
maxLR_H0_2
.....
maxLR_H0_9998
maxLR_H0_9999

9999 simulated null data

Order from big to small

If higher ranking value to higher statistics, p-value is 1-rank/10000.
OB in-house tool for LRT method

Signal Detection with LRT
A Tool To Help You Decide

Signal Detection Using LRT Method

LRT: The Right Tool for the Right Job

Quick Start Guide

Developed by Ted Guo, Lan Huang, Jyoti Zakkakar and Ram C. Tiwari of Office of Biostatistics/CDER/FDA, this tool (software solution) named LRT is aimed to help FDA’s medical and statistical reviewers detect potential adverse events that are statistically associated with the drug of interest. In doing so, the false-positive rate is controlled at the 5% significance level.

This tool also helps detect harmful drugs associated with the adverse event of interest. The false-positive rate is controlled in the same manner.

User: Please follow the instructions on the next screen. You will be able to define and fine-tune your own analysis.
### Example (Myocardial infarction)

<table>
<thead>
<tr>
<th>PT</th>
<th>#Drug</th>
<th>n.j</th>
<th>PRR025 (&gt;1)</th>
<th>sB05 (&gt;2)</th>
<th>BCPNN025 (&gt;0)</th>
<th>EB05 (&gt;2)</th>
<th>LRT (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1416</td>
<td>26,848</td>
<td>242</td>
<td>36</td>
<td>137</td>
<td>35</td>
<td>51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>#Drug (Generic)</th>
<th>Nij</th>
<th>PRR025 (&gt;1)</th>
<th>LRT (P&lt;0.05)</th>
<th>sB05 (&gt;2)</th>
<th>BCPNN025 (&gt;0)</th>
<th>EB05 (&gt;2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rosiglitazone</td>
<td>2231</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>Metformin And Rosiglitazone</td>
<td>322</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>Calcium Chloride And Glucose And Magnesi</td>
<td>637</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>Clopidogrel</td>
<td>419</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5</td>
<td>Rosuvastatin</td>
<td>398</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6</td>
<td>Atorvastatin</td>
<td>506</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>7</td>
<td>Calcium Chloride And Icodextrin And Magn</td>
<td>150</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>8</td>
<td>Ticagrelor</td>
<td>109</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>9</td>
<td>Glimepiride And Rosiglitazone</td>
<td>46</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>10</td>
<td>Glyceryl Trinitrate</td>
<td>175</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
## LRT to longitudinal LRT (Motivation)

<table>
<thead>
<tr>
<th>LRT</th>
<th>Longitudinal LRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count data</td>
<td>Count data with exposure information</td>
</tr>
<tr>
<td>Large post-market observational safety data</td>
<td>Observational or clinical trial data</td>
</tr>
<tr>
<td>Drug signals for one AE</td>
<td>Same</td>
</tr>
<tr>
<td>Or AE signals for one drug</td>
<td></td>
</tr>
<tr>
<td>Multiple AEs and drugs</td>
<td>Same</td>
</tr>
<tr>
<td>Fixed time analysis</td>
<td>Same</td>
</tr>
<tr>
<td>Analysis over time using cumulative count data without planned alpha control</td>
<td>Use alpha-spending for analysis over time</td>
</tr>
<tr>
<td>covariate adjustment by stratification</td>
<td>same</td>
</tr>
</tbody>
</table>
Longitudinal LRT method (sequential LRT) for active surveillance

• General
  – Compare multiple AEs by drug
  – Compare two drugs for one AE of interest (1st occurrence or without recurrence)
  – Compare multiple drugs for one AE of interest (may have recurrence or combined AE terms)

• Control error rates and false discovery rate (FDR)
Define countable cases and drug exposure

- Countable cases: AEs that occur during the exposure period (other definitions: AEs occur several days after the drug exposure)

- Drug exposure
  - Event-time
  - Person-time
  - Exposure-time

- Time
  - calendar time
  - time after drug exposure
Definition of event-time
Definition of person-time

s=1

\[ P_{i=1,js} \]

AE 1

s=2

\[ P_{i=1,js} \]

AE 1

s=3

\[ P_{i=1,js} \]
Definition of exposure-time
### Working data structure (with event-time)

<table>
<thead>
<tr>
<th></th>
<th>Drugs</th>
<th></th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>n11</td>
<td>...</td>
<td>n1j</td>
</tr>
<tr>
<td>2</td>
<td>n21</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>i</td>
<td>...</td>
<td>...</td>
<td>nij</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>I</td>
<td>nl1</td>
<td>...</td>
<td>nlj</td>
</tr>
<tr>
<td>Col total</td>
<td>n.1</td>
<td>...</td>
<td>n.j</td>
</tr>
</tbody>
</table>

J=14 in the above table. At look k (k=1,…, K=5), there are two tables constructed from the individual level data. Pij is the event-time (unit here is day) for the AE i and drug j. We suppress k in the notation.
Exposure-based longitudinal LRT Methods using event-time

\[ n_{ijk} \sim \text{Poisson}(p_{ijk} \times P_{i.k}), \]

\[ (n_{.jk} - n_{ijk}) \sim \text{Poisson}(q_{ijk} \times (P_{.k} - P_{i.k})) \]

\[ i = 1, \ldots, I, \ j = 1, \ldots, J, \ K = 1, \ldots, K. \]

H0: \( p_i = q_i \) over \( i = 1, \ldots, I \), if \( J \) (drug) is fixed.
RR\( i = p_i / q_i = 1 \) under H0, \( i = 1, \ldots, I \), which is relative event-rate of ith AE vs. other AEs for fixed drug j.
The likelihood ratio is then

\[
LR_{ijk} = \frac{\left( \hat{P}_{ijk, H_a} \right)^{n_{ijk}} \left( \hat{q}_{ijk, H_a} \right)^{n_{jk} - n_{ijk}}}{\left( \hat{P}_{ijk, H_0} \right)^{n_{jk}}}
\]

\[
LR_{ijk} = \frac{\left( \frac{n_{ijk}}{P_{i.k}} \right)^{n_{ijk}} \left( \frac{n_{jk} - n_{ijk}}{P_{..k} - P_{i.k}} \right)^{n_{jk} - n_{ijk}}}{\left( \frac{n_{jk}}{P_{..k}} \right)^{n_{jk}}}
\]

\[
= \left( \frac{n_{ijk}}{E_{ijk}} \right)^{n_{ijk}} \left( \frac{n_{jk} - n_{ijk}}{n_{jk} - E_{ijk}} \right)^{n_{jk} - n_{ijk}} ; E_{ijk} = \frac{n_{jk} \times P_{i.k}}{P_{..k}}
\]

Test statistic is

\[
\max LR_{jk} = \max_i LR_{ijk} , i = 1, \ldots, I
\]
Working data structure (with person-time)

AE of interest

\[ J = 1 \]

<table>
<thead>
<tr>
<th>drug</th>
<th>( n_{11k} )</th>
<th>( n_{21k} )</th>
<th>( n_{1.1k} = n_{11k} + n_{21k} )</th>
<th>( P_{11k} )</th>
<th>( P_{21k} )</th>
<th>( P_{..} = P_{11k} + P_{21k} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>l=2</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Col</td>
<td></td>
<td></td>
<td>( n_{1.1k} = n_{11k} + n_{21k} )</td>
<td></td>
<td></td>
<td>( P_{..} = P_{11k} + P_{21k} )</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sequential LRT (with person-time)

\[ n_{11k} \sim \text{Poisson}(p_{11k} \times P_{11k}), \]
\[ (n_{21k}) \sim \text{Poisson}(q_{21k} \times P_{21k}) \]

\[ n_{11k} \mid n_{1k} \sim \text{Binomial}(n_{1k}, \frac{RR_{11k} P_{11k}}{RR_{11k} P_{11k} + (P_{21k})}) \]

H0: \( p_1 = q_2 \), Ha: \( p_1 > q_2 \)

RR\(_1\) = \( p_1 / q_2 \), is relative risk of ith AE vs. the other AE for fixed drug j; or relative risk of ith drug vs. the other drug for fixed AE j.
The likelihood ratio is then

\[
LR_{11k} = \frac{(\hat{p}_{11k}, H_a)^{n_{11k}} (\hat{q}_{11k}, H_a)^{n.1k-n_{11k}}}{(\hat{p}_{11k}, H_0)^{n.1k}}
\]

\[
LR_{11k} = \frac{\left(\frac{n_{11k}}{P_{11k}}\right)^{n_{11k}} \left(\frac{n_{21k}}{P_{21k}}\right)^{n_{21k}}}{\left(\frac{n_{11k} + n_{21k}}{P_{11k} + P_{21k}}\right)^{n_{11k} + n_{21k}}}
= \left(\frac{n_{11k}}{E_{11k}}\right)^{n_{11k}} \left(\frac{n_{21k}}{n.1k - E_{11k}}\right)^{n_{21k}}; E_{11k} = \frac{n.1k \times P_{11k}}{P_{11k} + P_{21k}}
\]

Test statistic is \( \max LR_{jk} = \max_i LR_{ijk}, i = 1,2. \)
Relationship seqLRT with CSSP and maxSPRT

- CSSP statistic is the number of adverse events. seqLRT statistic is maxLR; same null data simulation process and assumption

- For maxSPRT: Let $n_{.k}=n_{1.1k}$ be the total # cases up to time-interval $k$. $n^{\text{drug}}_{k}=n_{1.1k}$ is the # cases for drug $i=1$.

$$E_{1.1k} = \frac{n_{.1k} \times P_{1.1k}}{P_{1.1k} + P_{2.1k}} = \frac{n_{.k}}{M + 1}$$

$$LRT_k = \frac{n_{.k}}{n^{{\text{drug}}}_k} \left( \frac{n^{{\text{drug}}}_k - n^{{\text{drug}}}_{.k}}{n^{{\text{drug}}}_k} \right) \left( \frac{1}{M + 1} \right)^{n^{{\text{drug}}}_k} \left( \frac{M}{M + 1} \right)^{n_{.k} - n^{{\text{drug}}}_{.k}}$$
Working data structure (with exposure-time)

<table>
<thead>
<tr>
<th>drugs</th>
<th>Jth AE</th>
<th>1</th>
<th>n_{1j}</th>
<th>1</th>
<th>P_1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>...</td>
<td>2</td>
<td>P_2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i</td>
<td>n_{dj}</td>
<td>i</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l</td>
<td>n_{Dj}</td>
<td>l</td>
<td>P_D</td>
</tr>
<tr>
<td></td>
<td>Col total</td>
<td>n_{j}</td>
<td></td>
<td>Col total</td>
<td>P.</td>
</tr>
</tbody>
</table>

Longitudinal LRT
(with exposure-time)

For a fixed  j* th AE, Assume  \( p_{d j^* s} = p_{d j^*} \).

The dist of the events: \( n_{d j^* s} \sim \text{ind Poisson}(p_{d j^*} P_{ds}) \)

\[
n_{d j^*} = \sum_s n_{d j^* s} \sim \text{ind Poisson}(p_{d j^*} P_d), P_d = \sum_s P_{ds}.
\]

\[
(n_{j^*} - n_{d j^*}) \sim \text{ind Poisson}(q_{d j^*}(P - P_d))
\]

\[
RR_{d j^*} = \frac{p_{d j^*}}{q_{d j^*}} \text{ is relative risk of } j^* \text{ th AE for drug } d \text{ vs. other drugs}
\]

Test is \( p_d=q_d \) over \( d=1,..,D \) if J (AE) is fixed

\( RR_d=p_d/q_d \), \( i=1,\ldots,D \) is relative risk of dth drug vs. other drugs for fixed AE j*.
The likelihood ratio is then

\[
LR_{djk^*} = \frac{\left(\hat{P}_{djk^*,H_a}\right)^{n_{jk}} \left(\hat{Q}_{djk^*,H_a}\right)^{n_{jk} - n_{djk}}}{\left(\hat{P}_{djk^*,H_0}\right)^{n_{jk}}}
\]

\[
LR_{djk^*} = \frac{\left(\frac{n_{djk^*}}{P_{dk}}\right)^{n_{djk^*}} \left(\frac{n_{j^*k} - n_{djk^*}}{P_k - P_{dk}}\right)^{n_{j^*k} - n_{djk^*}}}{\left(\frac{n_{j^*k}}{P_k}\right)^{n_{jk}}}
\]

\[
= \left(\frac{n_{djk^*}}{E_{djk^*}}\right)^{n_{djk^*}} \left(\frac{n_{j^*k} - n_{djk^*}}{n_{j^*k} - E_{djk^*}}\right)^{n_{j^*k} - n_{djk^*}}, \quad E_{djk^*} = \frac{P_d \times n_{j^*k}}{P_k}
\]

Test statistic is

\[
\max_j \max_d LR_{jk} = \max_d LR_{djk}, \quad d = 1, \ldots, D
\]
Distribution of LRT under H0

- Test Statistic is MaxLR$_{jk}$ (discussed in earlier slides)
- The distribution of MaxLR$_{jk}$ under H0 is not analytically tractable
- We use Monte Carlo method to obtain the empirical dist for each k
- Cases can be generated “cumulatively’ using multinomial distribution.
- Cases can also be generated using multinomial for each individual time-period and then summing-up over time
Null data generation (cumulatively)

For event-time and person-time cases

\[(n_{1jk},...,n_{ljk}) \mid n_{jk} \sim \text{Multinomial}(n_{jk},(\frac{P_{1,k}}{P_{..}},...,\frac{P_{l,k}}{P_{..}})), i = 1,\ldots, I.\]

I is the total # of AEs or drugs under comparison.

For exposure-time cases,

\[(n_{1j*k},...,n_{Dj*k}) \mid n_{j*k} \sim \text{Multinomial}(n_{j*k},(\frac{P_{1,k}}{P_{k}},...,\frac{P_{Dk}}{P_{k}})), d = 1,\ldots, D.\]

D is total # of drugs under comparison.

The parameters in the multinomial distribution are from the observed data.
P-value calculation (for each period k)

- Calculate MaxLR from observed data (one) over time (k=1, 2, 3,…, K)

- Calculate MaxLRs from the 9,999 simulated null data for each time period

- At each time period, compare the observed MLR and the ones from simulation \(\rightarrow\) p-value = 1-rank of the observed maxLR among the 10000 maxLRs.

- If p-value < alpha(k) \(\rightarrow\) reject H0 and identify signals
Alpha-Spending Functions and Decision Rules

- Specify the error rate to be spend at look $k=1,...,K$. This can be monotonic power functions such as alpha spending functions:

$$\alpha(k) = \frac{1}{K} \alpha$$
$$\alpha(k) = \alpha \frac{1}{2^k}$$

$$cum\alpha(k) = \frac{k}{K} \alpha \leq \alpha$$
$$cum\alpha(k) = \alpha \sum_{r=1}^{k} \frac{1}{2^r} \leq \alpha$$

The second formulation does not depend on K.
Alpha-Spending Functions and Decision Rules

- Other choices of alpha-spending boundary functions are: O’Brien-Fleming, Pocock, Lan-DeMets, etc.

- At look k, the AE associated with the maxLR in the obs data is a signal for the particular drug if the p-value is < alpha(k).

- There could be secondary signals with next lower ordered values of LR, after maxLR, in the observed data, that have p-value <alpha(k): LR2, LR3….. (step-down procedure).
Application of LRT methods to Pooled clinical trial data for PPIs

- PPIs are a class of drugs that decrease gastric acid secretion through inhibition of the proton pump. It helps in the secretion of acid from the stomach glands.

- In a recent study, it has been found that proton pump inhibitors (PPIs) are associated with increased risk of hip fractures (side effect) (Yang et al. 2006). The increased risk of hip fractures is attributed to osteoporosis caused by proton pump inhibitors.

- Pooled clinical trial data from FDA/OTS/OCS legacy database

- PPIs were concomitantly used with test drugs for treating osteoporosis among targeted patients.
Application of LRT methods to Pooled clinical trial data for PPIs

- Pooled data with 10 trials (sample sizes from hundreds to thousands). # Subjects using concomitant PPIs is about 10% of the total sample size.

- A total of 14 drugs (7 test drugs, and 7 test drug+PPIs) are included in the exploration.


- Alpha=0.05

- With alpha(k)=alpha/2*k, alpha(1)=0.025, alpha(2)=0.0125, alpha(3)=0.00625, alpha(4)=0.003125, alpha(5)=0.001563.
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<th>3</th>
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<td>4.1</td>
<td>2.3</td>
<td>4.4</td>
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<td>6.8</td>
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<tr>
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<td>3.9</td>
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<td></td>
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</table>
Comparison of PL vs. PL+PPIs (I=2) using Sequential LRT method (person-time)

• AE of interest is a composite AE (AEOST) including many AE terms associated with osteoporosis (J=1), 1st occurrence of AEOST.

• PL+PPIs vs. PL (I=2)

• Sample sizes $N_{dotj}$ for $j=1$ are 57, 163, 232, 439, and 500 for analysis periods 1, 2, 3, 4, and 5, respectively.

• $Rr$ values are 4.7, 2.4, 2.5, 1.9, 1.7 for $k=1$ to 5.

• When $k=1$, the p-value from seqLRT is 0.001. PL+PPIs had higher relative risk vs. PL for AEOST ($<\alpha(1)=0.025$), stop the search by sequential method.
Safety signals for multiple occurrences of AEOST (PL+PPIs vs. PL, I=2) by longLRT (exposure-time)

<table>
<thead>
<tr>
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<td>rr</td>
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<td>2.9</td>
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<td>2.4</td>
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</table>

PL+PPIs is a signal for AEOST for k=1 to 5 periods.
Do not stop monitoring the signals over time.
Safety signals for multiple occurrences of AEOST (l=14 drugs) by longLRT (exposure-time)

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<th>4</th>
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<td>0</td>
<td>0</td>
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<td>Lasoxifene+ PPIs</td>
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<td>2</td>
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<td>Lasoxifene+ PPIs</td>
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<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH+PPIs</td>
<td>rr</td>
<td>5.9</td>
<td>2</td>
<td>2.3</td>
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<tr>
<td>PTH+PPIs</td>
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<td>Bazedoxifen e+PPIs</td>
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<td>0.99</td>
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Discussion

- One AE or multiple AEs, one drug and multiple drugs
- Drug class and AE group
- Count data or data with exposure
- Fixed time analysis or analysis over time
- Rate and risk
- Different definitions of exposure
- Method for incorporating the study effect
References


• Noren et al. 2010 (See Lecture # 1)


Appendix
Exposure-based longitudinal Methods

• Binomial LRT

\[
LRT_k = \frac{\left( \frac{n_{ijk}}{P_{i,k}} \right)^{n_{ijk}} \left( 1 - \frac{n_{ijk}}{P_{i,k}} \right)^{n_{i,k}-n_{ijk}} \left( \frac{n_{.jk} - n_{ijk}}{P_{.k} - P_{i,k}} \right)^{n_{.jk} - n_{ijk}} \left( 1 - \frac{n_{.jk} - n_{ijk}}{P_{.k} - P_{i,k}} \right)^{n_{.k} - n_{.jk} - n_{i,k} + n_{ijk}}}{\left( \frac{n_{.jk}}{P_{.k}} \right)^{n_{.jk}} \left( 1 - \frac{n_{.jk}}{P_{.k}} \right)^{n_{.k} - n_{.jk}}}
\]

→ Poisson, LRT
Notations for the following plots on drug exposure

- * Indicates start date of drug j (or d) and ** indicates stop date of drug j (or d).

- Assume that each subject takes a single drug (or drug combination); different subject may take different drugs or drug combinations.

- Circled dots indicate occurrences of AEs (AE i, i=1, 2, 3,.....). Only AEs between * and ** are countable cases and are shown in the plots over time.

- $P_{1_{ij}s}$ is the event-time for sth subject taking jth drug and having 1st occurrence of ith AE. $P_{2_{ij}s}$ is the event-time for sth subject taking jth drug and having 2nd occurrence of ith AE.

- $P_{ij}s$=$P_{1_{ij}s}$ is the event-time for sth subject taking jth drug and having 1st occurrence of ith AE, which is also person-time when we only consider AE without recurrence or the 1st occurrence of one AE with repeated occurrences

- $P_{ds}$ is the exposure-time for sth subject taking dth drug and having multiple AEs during the exposure duration
Exposure for ith AE and jth (dth) drug
(aggregation of subject-level information)

For event time, \[ P_{ij} = \sum_{s} \sum_{l(i,s)} P_{ijs}^{l(i,s)}, \ s = 1, ..., S; l(i, s) = 1, ..., L(i, s). \]

S is the total # of subjects, and L(i,s) is the total # of occurrences of ith AE for sth subject.

\[ P_{i\cdot} = \sum_{j} P_{ij}, \ P_{\cdot j} = \sum_{i} P_{ij}, \ P_{\cdot \cdot} = \sum_{i} \sum_{j} P_{ij}. \]

For person-time, \[ P_{ij} = \sum_{s} P_{ijs}. \]

For exposure-time, \[ P_{d} = \sum_{s} P_{ds}, \ P_{\cdot} = \sum_{d} P_{d} = \sum_{d} \sum_{s} P_{ds}. \]
Simulation using the information from the Pooled clinical trial data

• seqLRT for 1\textsuperscript{st} occurrence of AEOST (J=1), PL+PPIs vs. PL only (I=2)

\[ n_{ijk} \mid n_{jk} \sim \text{Binomial}(n_{jk}, \frac{RR_{ijk} P_{i.k}}{RR_{ij} P_{i.k} + (P_{..k} - P_{i.k})}) \]

• longLRT for any occurrences of AEOST (J=1), multiple drugs

\[
(n_{1*j*k}, ..., n_{D*j*k}) \mid n_{j*k} \sim \text{Multinomial}(n_{j*k}, (RR_{1j} r_{0} \frac{P_{1k}}{P_{.k}}, ..., RR_{Dj} r_{0} \frac{P_{Dk}}{P_{.k}})), d = 1, ..., D.
\]

\[ P_{.k} = \sum_{d} P_{dk}, \quad RR_{dj} \geq 1, \quad \sum_{d=1}^{D} RR_{dj} r_{0} \frac{P_{dk}}{P_{.k}} = 1. \]
Simulation setup

- For H0 data, $RR_{i1}=1$
- For Ha data, $RR_{i1}=c$ (PL+PPIs vs. PL).
  - $c=1.2, 1.5, 2, 4, 6, 10$
- Sample size as $z^*n_{1k}$
  - $c=1, 2, 4, 10$
- Simulation 1000 data for each case
Performance evaluation

• Conditional power:
  – \( \Pr(k) = \# \text{rejecting H0 at kth period}/1000, \ k=1, \ldots, 5. \)

• Unconditional power for seqLRT
  – \( \text{Power}(k) = pr(1) + \cdots + (1-pr(1)) \times \cdots \times (1-pr(k-1)) \times pr(k) \)

• When data is generated under H0, \( pr(k) \) is conditional error rate and power\( \rightarrow \) type-I error rate for seqLRT

• For longLRT without stopping the procedure, we use cumulative error rate \( \text{cumer}(k) = pr(1) + pr(2) \ldots + pr(k) \)
Patterns on error rate (rr=1 H0 data, z=1, similar for z=2, 4))

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<th></th>
<th></th>
<th></th>
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<td>ndotj</td>
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</tr>
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<td>232</td>
<td>439</td>
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<td>65</td>
<td>195</td>
<td>286</td>
<td>647</td>
<td>787</td>
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<tr>
<td>pr(k)</td>
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<td>0.012</td>
<td>0.007</td>
<td>0.003</td>
<td>0.001</td>
<td>0.018</td>
<td>0.005</td>
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<td>0.001</td>
</tr>
<tr>
<td>type-l</td>
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<td>0.039</td>
<td>0.045</td>
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<td>0.049</td>
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<tr>
<td></td>
<td>cumer(k)</td>
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<td>0.023</td>
<td>0.03</td>
<td>0.034</td>
<td>0.035</td>
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<tr>
<td>alpha(k)</td>
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<td>0.0375</td>
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</table>
Patterns on power (seqLRT), $z=1$, $\text{rr}=1.2$ to 4

Conditional power

Unconditional power
Patterns on power (seqLRT), rr=2, 
z=0.5 to 4

Conditional power  Unconditional power
Patterns on (conditional) power (longLRT)

$Z=1$, relative risk from 1.2 to 4

$RR=2$, $z$ from 0.5 to 4