Disproportionality statistics for signal detection

Andrew Bate
Senior Director, Analytics Team Lead, Epidemiology
ISOP-UMC Training Course
Mysore, 13 January 2015
Disclosures

- I am a full time employee of Pfizer and hold stocks and stock options
• Analysis of spontaneous reports of suspected adverse drug reactions (ADRs) is a valuable tool in the detection of previously unknown drug adverse adverse reactions.
• Reports of adverse events (AEs) associated with a drug are not necessarily true ADRs, that is, they may be temporally associated with a drug but not caused by the drug.
• Hypothesis generation of new possible side effects from such data is referred to as signal detection.
“Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.”

Ref CIOMS VIII  Practical Aspects of Signal Detection in Pharmacovigilance 2009
Spontaneous reporting limitations

- Often limited clinical information on reports and satisfactory secondary case evaluation is not always possible
- Not all ADRs that occur will be recognized as drug induced by a healthcare professional
- Even those that are suspected will not necessarily be reported
- Suspicion can mistakenly rest on the drug, coincidental spontaneous ADR case reports resulting
- Control information is not collected as part of spontaneously reported systems, the drug use is not known, and there is no direct information on disease incidence

Ref Bate et al 2008 FCP
Quantitative signal detection

- To detect potential signals for further investigation that are not readily recognisable on a single case report nor otherwise readily apparent at case entry
- Enhance rather than replace other methods of signal detection
  - E.g. Initial case review of spontaneous reports
- Overall help to detect signals earlier, more effectively and more efficiently
- Primarily useful in large data sets
Quantitative signal detection – different approaches

• Several methods for screening spontaneously reported data
• Most common approach: “measures of disproportionality”
• Different measures of disproportionality
• But all aim to detect the ‘unexpectedly’ frequently reported relative to a background of other reports
• Quantitative outputs clinically reviewed and some subsequently considered as ‘signals’
Metrics used in quantitative screening of spontaneous reports

2 by 2 contingency table

<table>
<thead>
<tr>
<th></th>
<th>AE of interest (y)</th>
<th>Other AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug of interest (x)</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Other drugs</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Proportional Reporting Ratio (PRR) =

\[
\frac{a \div (a + b)}{c \div (c + d)}
\]

Reporting Odds Ratio (ROR) =

\[
\frac{a \div b}{c \div d}
\]

Observed / Expected\(^1\) =

\[
\frac{a \div (a + b)}{(a + c) \div (a + b + c + d)}
\]

\(^1\) Frequentist basis of EBGM and IC

See Bate and Evans 2009 PDS, for an overview
Bayesian methods in quantitative signal detection

- Bayesian methods give framework for how to combine prior information with data
  - Prior information/knowledge + data
  - Account in a conceptually transparent way for external data and/or subjective opinion
- Bayesian methods - not always more complex

\[
IC \approx \log_2 \frac{\text{Observed} + 1/2}{\text{Expected} + 1/2}
\]

- High Observed and Expected, shrinkage no practical impact
- When Expected and Observed are low, IC tends to zero
- Note: Idea is that overall the estimates will be better – not that each estimate will necessarily be better
  - Informative priors also possible

Refs Noren et al 2013, for IC formula
Bate and Evans 2009 PDS, for an overview
Change in Information Component over time

Captopril - Coughing

Time (year)
Change in Information Component over time

Digoxin - Rash

Time (year)
Change in Information Component over time

Digoxin - Acne

Time (year)
Change in Information Component over time

Practolol, ATC C07AB - Peritonitis sclerosing

IC

Practolol
ATC C07AB

year

Differences in metrics

• No single best method
• PRR arguably most easy to interpret
• Shrinkage in Bayesian approaches advantageous at low counts, but more complex
  – Van Puijenbroek et al 2001
• Underreporting less effect for ROR than PRR
  – Van Der Heijden 2002, Rothman et al 2004
• ROR gives more volatile scores
**Choice of metrics**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>54</td>
<td>916</td>
</tr>
</tbody>
</table>

ROR = 4.24, PRR = 3.59, O/E = 3.33
Choice of metrics

ROR = 3.88, PRR = 3.59, O/E = 3.33
Ongoing Misunderstanding

• "The 'PRR' of 6 indicates that for this drug the risk of reporting this event is six times higher compared with reference drugs."

• Should be:

"The 'PRR' of 6 indicates that for this drug the probability of reporting this particular event rather than any other event is six times higher compared to the probability for reference drugs"
Background reading

- Norén GN, Hopstadius J, Bate A. 2013 Shrinkage observed to expected ratios for robust and transparent large scale pattern discovery. Statistical Methods in Medical Research. 22 (1), 57-69
Conclusions

• Several methods for screening spontaneously reported data
• Most common approach: “measures of disproportionality”
• Different measures of disproportionality
• But all aim to detect the ‘unexpectedly’ frequently reported relative to a background of other reports
• No one best method
• Quantitative outputs clinically reviewed and some subsequently considered as ‘signals’
• Quantitative signal detection needs to be part of robust overall signal management programme