PHARMACOVIGILANCE: STATISTICAL ASPECTS

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Limitations of Premarketing Clinical Trials

At the time of marketing approval, clinical trial data are available,

– on selected patients (with inclusion/exclusion criteria)
– on limited numbers of patients
– on patients treated for relatively short periods
– for controlled conditions
Limitations of Premarketing Clinical Trials

At the time of marketing approval, information is not available about

– patients with co-morbid illnesses
– patients using concomitant medications
– patients with chronic exposure
– patients from various geographical places
– rare but serious adverse events
Why Pharmacovigilance is Required?

- In 1970, Dunlop observed that
  
  “No drug, which is pharmacologically effective, is without hazard. Furthermore, not all hazards can be known before a drug is marketed”.


  Monitoring the safety of medicines is vital throughout their marketed life
Pharmacovigilance and Its Objective

Pharmacovigilance is defined as a science concerned with detection, assessment, understanding and prevention of adverse reaction to medicine with the main objectives:

- Proactive monitoring and reporting on the safety of drugs
- Assessment of the risks and benefits of marketed medicines
Pharmacovigilance and Its Objective

- Monitoring the impact of any corrective actions taken
- Providing information to consumers, practitioners and regulators on the effective use of drugs
- Designing programs and procedures for collecting and analyzing reports from patients and clinicians

To improve the safe and rational use of medicine and consequently, improving patient care and public health
How is Pharmacovigilance Done?

- **Passive surveillance:**
  - Spontaneous reports
  - Case series
- **Active surveillance**
  - Sentinel sites
  - Drug event monitoring
  - Registries
- **Comparative observational studies**
  - Cross-sectional study (survey)
  - Case-control study
  - Cohort study
- **Targeted clinical investigations**
Various Databases of Adverse Drug Reaction Reports

- **US FDA Spontaneous Report System AERS**
  - Post-Marketing Surveillance of all Drugs since 1969
  - ADR Coding System MedDRA

- **World Health Organization VIGIBASE**
  - The largest and most comprehensive database
  - Includes Data from many Countries
  - Developed and maintained by the UMC
  - ADR Coding System WHOART

- **European pharmacovigilance database EVDBMS**
  - Created by the EMEA in December 2001
  - Contains adverse reaction reports to medicines licensed across the EU
  - ADR Coding System EVMPD
What is A Safety Signal?

- A safety signal refers to ‘reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously’

- An apparent excess of adverse events compared to what would be expected to be associated with use of a product

Safety signal = a concern about an excess of adverse events compared to what would be expected to be associated with a product's use

- Even a single well-documented case report may be viewed as a safety signal
Various Methods of Obtaining Safety Signals from Databases

- Traditional way
- Data mining using Measures of Disproportionality
Traditional Way

- Traditional way is the medical evaluation of case reports individually
What is Data Mining

- Systematic examination of the reported adverse events by using statistical / mathematical tools
- Generates statistical values or scores
- These scores indicate the strength of the association between a drug of interest and an event in the database: the higher the score, the stronger the statistical association
- These scores are used to alert safety evaluators for potential safety issues, including actual safety signals
Data Mining - Measures of Disproportionality

A two-by-two tables are the scaffold for disproportionality (DPA) analysis.

<table>
<thead>
<tr>
<th>Counts reports of</th>
<th>With drug i</th>
<th>Without drug i</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>With event j</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Without event j</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>
Measures of Disproportionality

Relative Reporting Ratio (RRR)

• The overall proportion of reports having event j is 
\[ \frac{a+b}{a+b+c+d}, \]

• If there are \((a+c)\) reports involving drug i, the expected number of reports of drug i with event j would be (assuming no association of report i with event j)
\[ e = \frac{(a+c)(a+b)}{(a+b+c+d)} \]

• The Relative Reporting Ratio “RRR”
\[ = \frac{a}{e} = \frac{a}{(a+b)(a+c)/(a+b+c+d)} \]
Measures of Disproportionality

Proportional Reporting Ratio (PRR)

- Commonly used measure in pharmacovigilance

$$PRR = \frac{a/(a+c)}{b/(b+d)}$$

$$SE(Ln\ PRR) = \sqrt{\left(\frac{1}{a} - \frac{1}{a+c} + \frac{1}{b} + \frac{1}{b+d}\right)}$$

$$95\%\ CI = \exp(Ln(PRR) \pm 1.96 \times SE(Ln\ PRR))$$
Measures of Disproportionality

Reporting Odds Ratio (ROR)

- Another measure of disproportionality

\[ \text{ROR} = \frac{a/c}{b/d} = \frac{ad}{bc} \]

\[ \text{SE}(\ln \text{ROR}) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \]

95% CI = exp(\ln(ROR) \pm 1.96 \times \text{SE}(\ln \text{ROR}))
Data Mining - Criteria to Define A Safety Signal

• A value of 1 for any of these measures ⇒ No association between the reporting of drug i and event j in the database

• A threshold is chosen and if the score exceeds this threshold, this gives the potential safety signal

• The commonly used thresholds to detect safety signals are a trade-off between two conflicting options: either generating too many false positive safety signals (less specific) if threshold is too low or missing true safety signals (less sensitive) if this threshold is too high

• The need for efficiency must be balanced against the cost of missing any true safety signal
Sensitivity and Specificity

Sensitivity = \frac{\text{Total no. of drug-event combinations having association which showed a safety signal}}{\text{Total no. of drug-event combinations having association}} \times 100

Specificity = \frac{\text{Total no. of drug-event combinations not having association which did not show a safety signal}}{\text{Total no. of drug-event combinations not having association}} \times 100
Data Mining - Measures of Disproportionality

Advantages

• Easy to calculate
• Simple to interpret
Data Mining - Measures of Disproportionality

Disadvantages

• These ratios have very large sampling variation with small number of reports

• Problem of multiple comparison
Data Mining - Measures of Disproportionality

The above issues can be resolved using following approaches:

– The Frequentist Approach
– The Bayesian Approach
The Frequentist Approach

- Compute the $\chi^2$ values for association in conjunction with the ratios
- Large ratios with non-significant $\chi^2$ are ignored
## The Frequentist Approach: Example

<table>
<thead>
<tr>
<th></th>
<th>AE</th>
<th>No AE</th>
<th>RRR</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>1</td>
<td>5</td>
<td>1.67</td>
<td>0.33</td>
</tr>
<tr>
<td>No Drug</td>
<td>5</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>No AE</td>
<td>RRR</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Drug</td>
<td>20</td>
<td>100</td>
<td>1.67</td>
<td>6.58</td>
</tr>
<tr>
<td>No Drug</td>
<td>100</td>
<td>980</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AE</td>
<td>No AE</td>
<td>RRR</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Drug</td>
<td>200</td>
<td>1000</td>
<td>1.67</td>
<td>65.8</td>
</tr>
<tr>
<td>No Drug</td>
<td>1000</td>
<td>9800</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data mining - Criteria to Define A Safety Signal: An Example

Eudravigilance data analysis system

• When PRR is displayed with 90% CI
  – Lower limit of 90% CI > 1
  – Number of cases ≥ 3

• When PRR is displayed with Chi$^2$
  – PRR ≥ 2
  – $\chi^2$ ≥ 4
  – Number of cases ≥ 3
The Bayesian Approaches

- A well-known effect of this framework is the phenomenon of shrinkage.
- These methods produce “shrinkage” values of disproportionality statistic, so that the raw values of reporting ratios (n/e) are transformed toward the common population mean by an amount that depends on the variability of the disproportionality statistic.
- Requires a prior distribution.
Bayesian Approach: Multiple Gamma Poisson Shrinker (MGPS) Approach

- The Bayesian Shrinkage model based on the mixture of two Gamma distributions
- This approach uses a measure called the Empirical Bayes Geometric Mean (EBGM), the expected value being calculated by a weighted estimate of different strata, where the expected value is under the null hypothesis of independence between the drug and reaction and a 90% confidence interval (EB05, EB95)
Bayesian Approach: Multiple Gamma Poisson Shrinker (MGPS) Approach

- Estimate $\lambda_{ij} = \mu_{ij} / E_{ij}$, where $N_{ij} = \text{Poisson} (\mu_{ij})$

- Assume super population model for $\lambda$
  - Prior distribution is mixture of two Gamma distributions
  - Estimate the 5-parameter prior from all the $(N_{ij}, E_{ij})$ pairs

- Posterior distributions of each $\lambda_{ij}$ are used to create “Shrinkage” estimates
Bayesian Approach: The Bayesian Confidence Propagation Neural Network (BCPNN)

- The Bayesian Shrinkage model based on multinomial distribution
- The BCPNN methodology uses a neural network architecture to measure dependencies between drugs and adverse reactions
- The BCPNN can be used to detect unexpected patterns in the data and to examine how such patterns vary over time
- The BCPNN uses a measure of disproportionality called the Information Component (IC)
Bayesian Approach: The BCPNN

- Information component and its variance can be calculated as

$$E(IC_{ij}) = \log_2 \frac{(N_{ij} + \gamma_{ij})(N + \alpha)(N + \beta)}{(N + \gamma)(N_{i.} + \alpha_{i})(N_{.j} + \beta_{j})}$$

$$V(IC_{ij}) = \frac{N - N_{ij} + \lambda - \lambda_{ij}}{(N_{ij} + \gamma_{ij})(1 + N + \gamma)} + \frac{N - N_{i.} + \alpha - \alpha_{i}}{(N_{i.} + \alpha_{i})(1 + N + \alpha)} + \frac{N - N_{.j} + \beta - \beta_{i}}{(N_{.j} + \beta_{j})(1 + N + \beta)} \frac{(\log 2)^2}{(log 2)^2}$$
Bayesian Approach: The BCPNN

• A positive IC value indicates that a particular drug-ADR combination is reported to the database more often than expected from the rest of the reports in the database.

• An IC value of zero means that there is no quantitative dependency.

• A negative IC value indicates that the combination is occurring less frequently than statistically expected in the database.
Data mining - Criteria to Define A safety Signal

Other Factors to Consider

• Regardless of whether ranking or a threshold is used for the scores, some reports are likely to be prioritized ahead of any others: For example just one new report of Torsade de pointes, QT prolongation, Stevens-Johnson syndrome, or a similar sentinel event is sufficient to flag a high priority for investigation

• To meet this need for different prioritization levels, a low threshold could be set for sentinel events, a slightly higher one for other serious events, and a third threshold for all other events
### Frequentist vs Bayesian

<table>
<thead>
<tr>
<th>Frequentist</th>
<th>Bayesian</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no rule for adjusting for the ‘multiple comparison’ problem</td>
<td>Addresses this issue</td>
</tr>
<tr>
<td>It results in a single relative reporting ratio that is easier to interpret without the added complexity of a separate $\chi^2$</td>
<td>Many different drug–event combinations in a single dimension for rankings and comparisons</td>
</tr>
</tbody>
</table>
## Conditions, advantages and disadvantages of different measures of disproportionality

Puijenbroek et al., Pharmacoepidemiology and drug safety 2002; 11: 3–10

<table>
<thead>
<tr>
<th>Measures of Disproportionality</th>
<th>Expected ‘null value’</th>
<th>Conditions</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROR-1.96SE</td>
<td>1</td>
<td>Cells a, b, c and d have to contain reports</td>
<td>Easily applicable</td>
<td>Cannot be calculated if $D_r$ is 0 &lt;br&gt; Interpretation difficult &lt;br&gt; Not reliable if small numbers in the cells</td>
</tr>
<tr>
<td>PRR-1.96SE</td>
<td>1</td>
<td>Cells a and c have to contain reports</td>
<td>Easily interpretation</td>
<td>SE can not always be calculated</td>
</tr>
</tbody>
</table>
# Conditions, advantages and disadvantages of different measures of disproportionality

<table>
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<th>Measures of Disproportionality</th>
<th>Expected ‘null value’</th>
<th>Conditions</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC-2SD</td>
<td>0</td>
<td>None</td>
<td>Always applicable</td>
<td>Relatively non-transparent for people not familiar with Bayesian analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Large number of calculations can be made</td>
<td>Only p-values provided</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can be used for pattern recognition in higher dimensions</td>
<td></td>
</tr>
<tr>
<td>Poisson</td>
<td>Only for rare events</td>
<td></td>
<td>Correction for different covariates can be easily established</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Always applicable</td>
<td></td>
</tr>
<tr>
<td>Chi square</td>
<td></td>
<td></td>
<td>Difficult to interpret</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of PRR and MGPS Methods

Comparative Performance of two quantitative safety signaling methods: implications for use in pharmacovigilance department: Almenoff et al., drug saf, 29, 876-87, 2006

- Greater confounding by demographic factor with PRR
- PRR gives more positive safety signals when number of reports is small
- PRR tends to be more sensitive and less specific than MGPS
Existing Methods for Safety Signal Detection in Various Regulators

- Multi-item Gamma Poisson Shrinker (MGPS) - US Food and Drug Administration (FDA)
- Bayesian Confidence Propagation Neural Network (BCPNN) - WHO Uppsala Monitoring Centre (UMC)
- Proportional Reporting Ratio (PRR) - UK Medicines Control Agency (MCA)
- Reporting Odds Ratios - Other national spontaneous reporting centers and drug safety research units
### Simpson’s Paradox

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Drug B</th>
<th>No Drug B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AE ‘X’</td>
<td>No ‘X’</td>
<td>AE ‘X’</td>
</tr>
<tr>
<td>Drug A</td>
<td>82</td>
<td>18</td>
<td>81</td>
</tr>
<tr>
<td>No Drug A</td>
<td>99</td>
<td>811</td>
<td>9</td>
</tr>
<tr>
<td>RR</td>
<td>4.58</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

From: Data Mining in Pharmacovigilence - Aimin Feng, David Madigan, and Ivan Zorych
Comparison of Stratified Empirical Bayesian (EB) and Crude Proportional Reporting Ratios (PRRs)

Effects of Stratification on Data Mining in the US Vaccine Adverse Event Reporting System (VAERS)

- Stratification revealed and reduced confounding in Empirical Bayesian and PRR
- Unmasked some vaccine-event pairs that the crude values did not highlight
- By decreasing the total number of highlighted vaccine-event pairs, stratification is likely to increase efficiency and might reduce workload
Stratification

- Confounders can pose as drug-event safety signals, stratify the database based on the confounders
- This will control the known confounders effect
- It may reduce the false positive and false negatives
- Potential variables for stratification: Age, Sex, Calendar year, the country of origin for a report etc

There should be balance between the amount of stratification which is feasible and the sensitivity/specificity of the safety signals generated as the individual tables become sparse by stratification
Data mining – Multiple Regression

• It computes the strength of a mathematical association between reports of an event and a drug after adjusting for the effects of other potential confounding factors

• Confounding factors, examples: other drugs, age group, gender etc.

• These methods are computationally intensive
Statistical Algorithms: Advantages

- Provide a safety net for human error as it is difficult to screen databases using conventional methods of pharmacovigilance.
- The value of using these methods is highest when scores alert the pharmacovigilance professionals about the unexpected, previously unknown and very rare adverse event.
Statistical Algorithms: Challenges

- Reports with missing information
- Reporting biases due to Unknown reporting mechanism
- Frequent non-causal associations with indications
- Co-morbidities
- Drug naming: Drug names entered into the system often have slight inconsistencies in spelling (drug name standardization)
- Duplicate reporting: Same report is submitted via different channels
Concluding Remarks

• Statistical analyses are useful tools in aiding early safety signal detection in spontaneous reporting systems.

• These statistical algorithms help users sort through several million potential combinations of drugs and events.

• They identify complex relationships not apparent by conventional approach.

• Investigators can prioritize investigations using statistical scores resulting in the best use of their resources.

• All of these approaches are inherently exploratory or hypothesis generating, but they may provide insights into the patterns of adverse events reported for a given product relative to products in the same class or to all other products.
Concluding Remarks

Remember

• These approaches are non clinical and only highlight deviations from independence.

• They do not explain whether these deviations are due to causal linkage between drug products and adverse event or due to some confounder.

• Hence they cannot replace the clinical reviewers/experts, but help them to prioritize their investigations.
Concluding Remarks

- When a drug product is new to the market and only a small number of reports have been received, it is more appropriate to assess these reports individually rather than based on statistical approaches as reliability of the statistical approach is questionable for small number of reports.

Safety signal detection = A Combination of Statistical Interpretation and Clinical Judgment
“As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality”

-Albert Einstein (1879-1955)
Reference Literature


Reference Literature
