

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”.

Committee on Safety of Drugs Report for 1969, (HMSO, London, 1971)



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

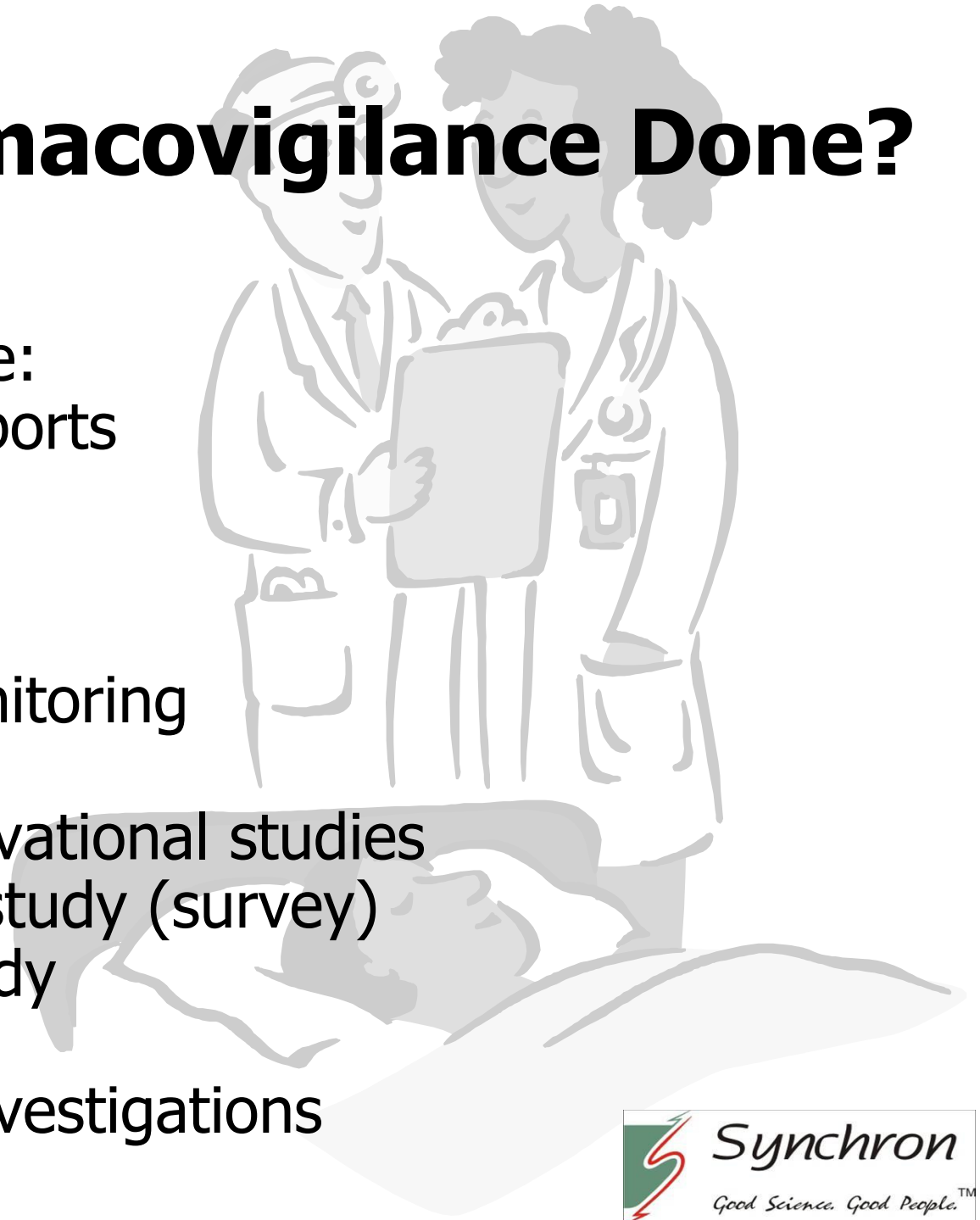
Pharmacovigilance and Its Objective

- 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

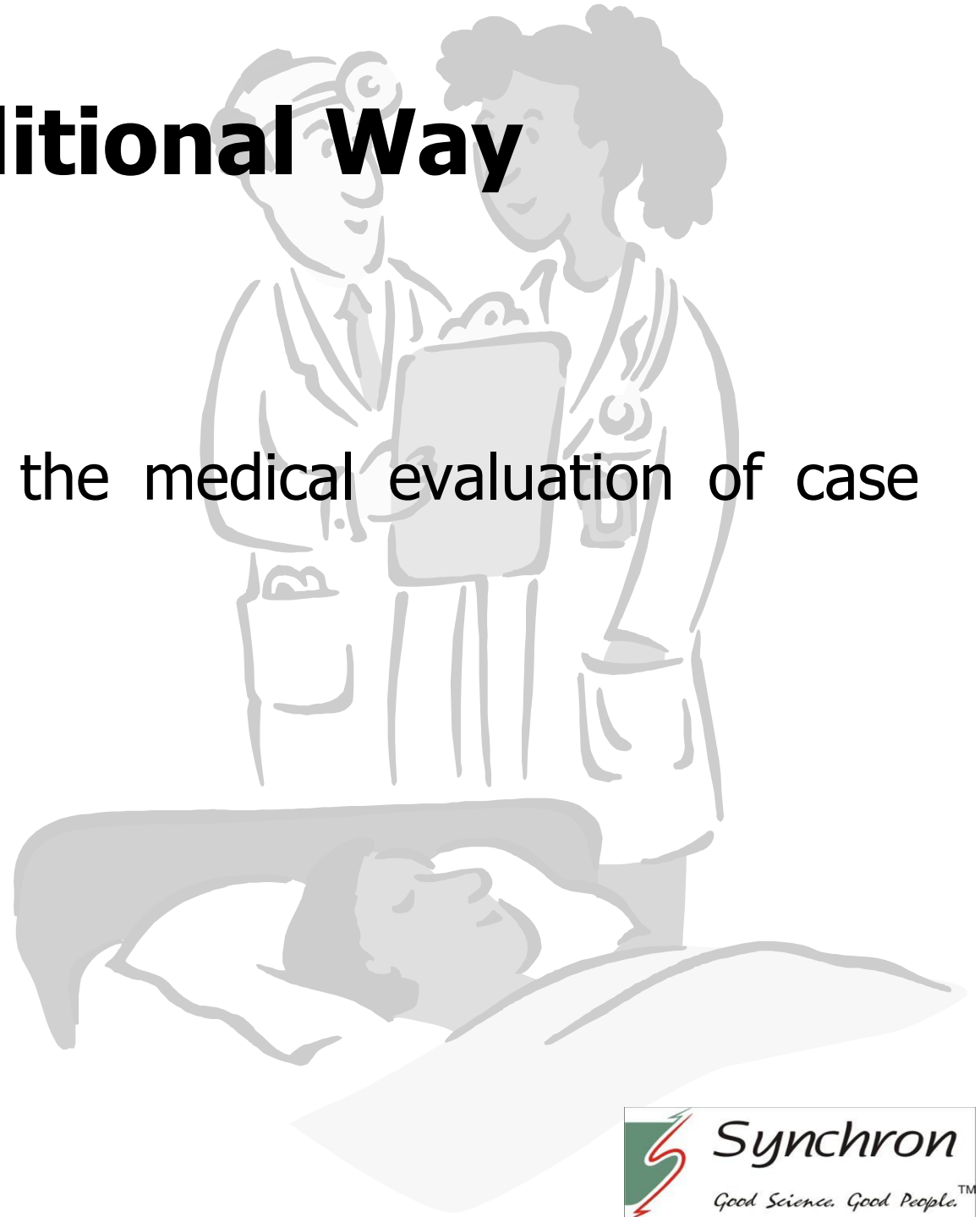
Various Methods of Obtaining Safety Signals from Databases

- 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

Counts of reports	With drug i	Without drug i	Total
With event j	a	b	$a+b$
Without event j	c	d	$c+d$
Total	$a+c$	$b+d$	$a+b+c+d$

Measures of Disproportionality

Relative Reporting Ratio (RRR)

- The overall proportion of reports having event j is $(a+b)/(a+b+c+d)$,
- 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)

$$e = (a+c)(a+b)/(a+b+c+d)$$

- The Relative Reporting Ratio "RRR"
 $= a/e = [a/(a+b)(a+c)/(a+b+c+d)]$

Measures of Disproportionality Proportional Reporting Ratio (PRR)

- Commonly used measure in pharmacovigilance

$$\text{PRR} = [a/(a+c)]/[b/(b+d)]$$

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

$$95\% \text{ CI} = \exp(\text{Ln}(\text{PRR}) \pm 1.96 * \text{SE}(\text{Ln PRR}))$$

Measures of Disproportionality Reporting Odds Ratio (ROR)

- Another measure of disproportionality

$$\text{ROR} = (a/c)/(b/d) = ad/bc$$

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

$$95\% \text{ CI} = \exp(\text{Ln}(\text{ROR}) \pm 1.96 * \text{SE}(\text{Ln ROR}))$$

Data Mining - Criteria to Define A Safety Signal

- A value of 1 for any of these measures \Rightarrow 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

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

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

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

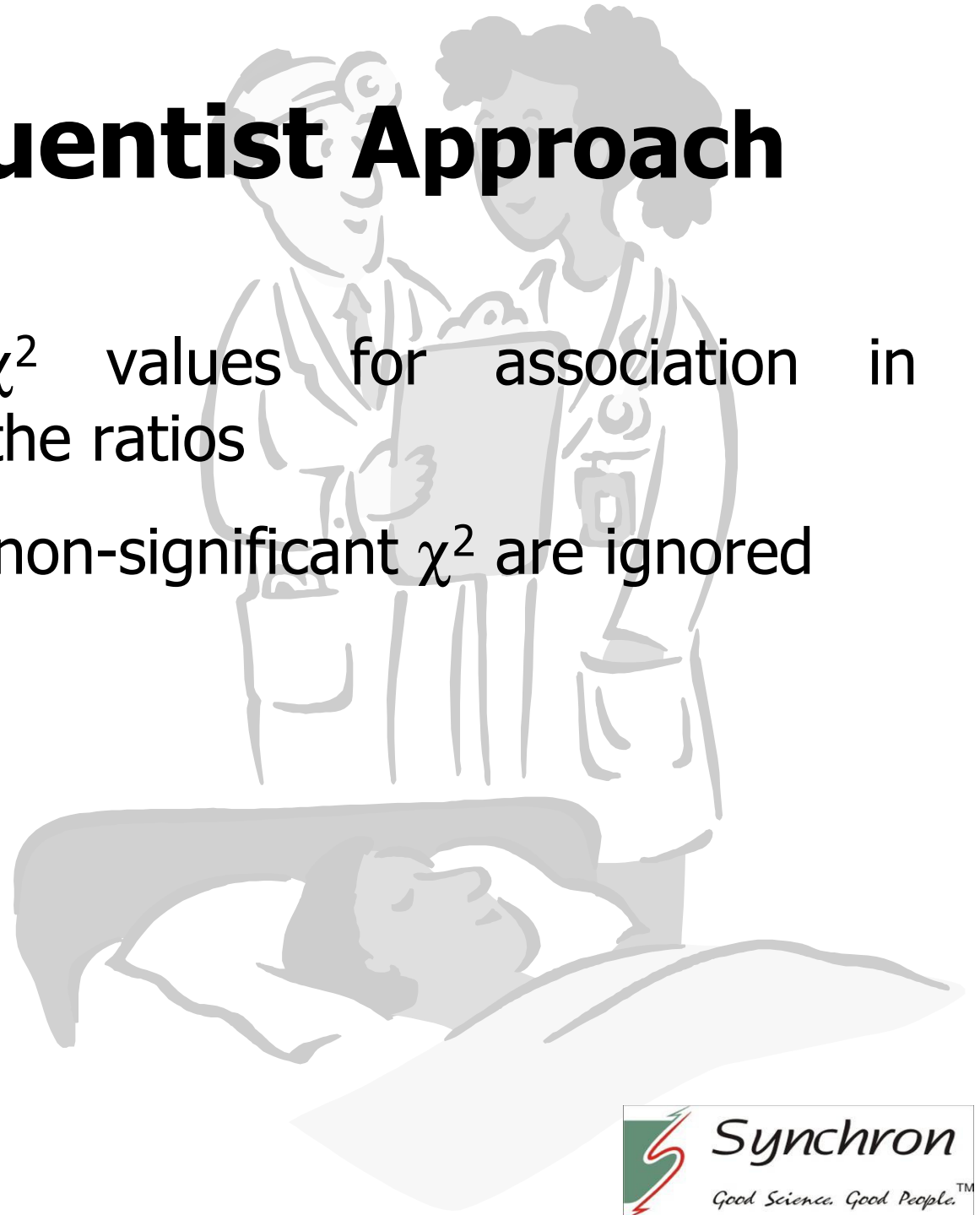
The above issues can be resolved using following approaches:

- The Frequentist Approach
- The Bayesian Approach



The Frequentist Approach

- Compute the χ^2 values for association in conjunction with the ratios
- Large ratios with non-significant χ^2 are ignored



The Frequentist Approach: Example

	AE	No AE	RRR	χ^2
Drug	1	5	1.67	0.33
No Drug	5	49		

	AE	No AE	RRR	χ^2
Drug	20	100	1.67	6.58
No Drug	100	980		

	AE	No AE	RRR	χ^2
Drug	200	1000	1.67	65.8
No Drug	1000	9800		

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 Chi²
 - PRR ≥ 2
 - $\chi^2 \geq 4$
 - 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 λ
 - 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 λ_{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

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

$$V(IC_{ij}) = \frac{\frac{N - N_{ij} + \lambda - \lambda_{ij}}{(N_{ij} + \gamma_{ij})(1 + N + \gamma)} + \frac{N - N_{i.} + \alpha - \alpha_i}{(N_{i.} + \alpha_i)(1 + N + \alpha)} + \frac{N - N_{.j} + \beta - \beta_i}{(N_{.j} + \beta_j)(1 + N + \beta)}}{(\log 2)^2}$$

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

Frequentist	Bayesian
There is no rule for adjusting for the 'multiple comparison' problem	Addresses this issue
	It results in a single relative reporting ratio that is easier to interpret without the added complexity of a separate χ^2
	Many different drug–event combinations in a single dimension for rankings and comparisons

Conditions, advantages and disadvantages of different measures of disproportionality

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

Measures of Disproportionality	Expected 'null value'	Conditions	Advantages	Disadvantages
ROR-1.96SE	1	Cells a, b, c and d have to contain reports	Easily applicable	Cannot be calculated if D^r is 0 Interpretation difficult Not reliable if small numbers in the cells
PRR-1.96SE	1	Cells a and c have to contain reports	Easily interpretation	SE can not always be calculated

Conditions, advantages and disadvantages of different measures of disproportionality

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

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 Regulatory Agencies

- 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

	Total		Drug B			No Drug B		
	AE 'X'	No AE 'X'	AE 'X'	No AE 'X'	AE 'X'	No AE 'X'	AE 'X'	No AE 'X'
Drug A	82	18	81	9	1	9		
No Drug A	99	811	9	1	90	810		
RR	4.58		1			1		

From: Data Mining in Pharmacovigilance - 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)

Woo et al, Drug Safety. 31(8):667-674, 2008.

- 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 can not replace the clinical reviewers/experts, but help them to priorities 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

Thank you

“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

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