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HANDOUT

Precision Methodologies:
Future of Signal Management

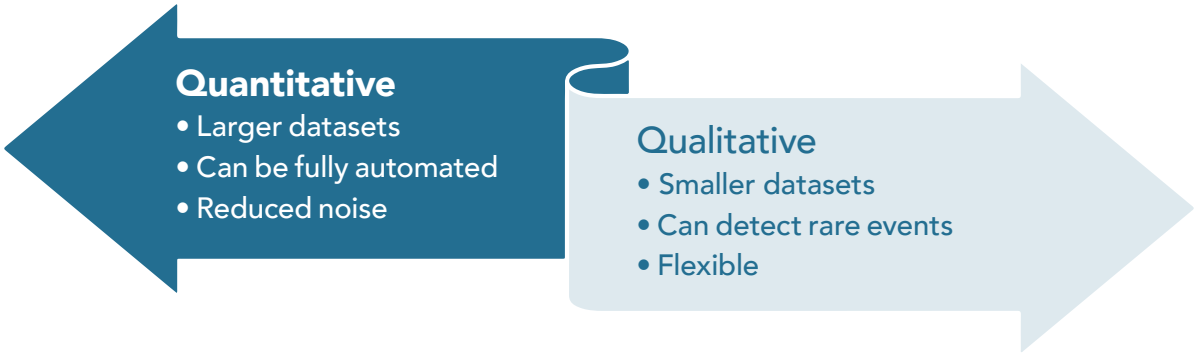
I. Signal detection methodologies and various steps

Key steps of a signal management process may include selection of signal review schedule, signal detection, signal validation, further assessment, and recommendation of action as applicable. These signals must be appropriately tracked and documented across the signal life cycle from detection through final action. Non- validated signals are closed at the validation step and signals with equivocal evidence may remain under monitoring for a certain period until further information is received to reach any conclusion.

Signal detection can be broadly performed by quantitative and qualitative review of the safety data.

Examples of Quantitative methods/data mining algorithms
• Proportional Reporting Ratio (PRR)
• Reporting Odds Ratio (ROR)
• Empirical Bayes Geometric Mean (EBGM)

Examples of Traditional Pharmacovigilance Methods
• Manual review
• Line listing/aggregate data review



Key limitations of quantitative methods	Key limitations of qualitative methods
• Rare ADRs can be missed	• Increased noise
• Not appropriate for smaller datasets	• More effort
	• Cannot be fully automated

As illustrated above, both quantitative and qualitative review have unique benefits and own set of limitations however, an effective process should involve a combination of the two or customisation of thresholds, frequent review of signal strategies and detailed review of data where necessary.

II. Sources of safety data and signals

- **Solicited sources:** clinical studies, organised data collection systems etc.
- **Unsolicited sources:** spontaneous reports, literature, internet/social media
- **Regulatory:** SUSARS/ICSRs received from regulatory authorities, EVDAS, FAERS

Signals notified by regulatory authorities

- **EMA:** PSUSA notifications, PRAC recommendations
- **FDA** has recently introduced the process of notifying newly identified safety signals to the respective MAHs

III. Precision methodologies

1. Patient characteristics

Pregnancy

- Involves review of parent & child reports, designing an appropriate MedDRA search strategy, retrieve missing information especially for the newly launched products
- Importance of the data quality and completion
- Challenges during assessment of long-term pregnancy outcomes

Paediatrics

- May require tailored statistical approaches, age sub-grouping and separate analysis with additional consideration of targeted medical events list

Geriatrics

- Key points to consider include polypharmacy and multiple co-morbidities, increased vulnerability, and impaired physiological elimination metabolisms

2. Safety surveillance during clinical trials

- Limited safety data
- Early detection of safety signals
- Review of signal strategies across the product life cycle

3. Product characteristics

Cell and gene therapy products

- Need for risk-based approach, complex and novel product types, review of product specific adverse effects such as genotoxicity, CRS etc.
- May require years of long term follow up

Biologics

- Importance of batch review and potentially emerging immunogenicity

Vaccines

- May require review of disease and population characteristics, signal strategies during mass vaccination

Medical devices

- Introduction of mandatory trends reporting in the EU-MDR

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Key points to consider

- The signal management process should allow heterogeneity and should be customisable.
- As stated in CIOMS VIII, selection of appropriate signal threshold is more important than the method of disproportionality.
- The use of complex algorithms may be particularly helpful in identifying true signals from the larger datasets and can be fully automated however, clinical assessment and selection of absolute case counts may be helpful where datasets are limited such as during clinical studies, rare diseases etc.
- Signal of disproportionality reporting (SDR) detected via complex algorithms must be supported by further evaluation and extended review of the safety data.

Glossary

- Designated Medical Events (DMEs) are the adverse events which are rare, serious or which are more likely to be associated with a high drug-attributable risk, e.g. Stevens-Johnson syndrome
- Targeted Medical Events (TME) are the events of special interest associated with medicinal products and/or patient populations
- Important Medical Events (IMEs) are a selected group of events that should be considered serious

Reference

1. SCOPE Work Package 5 Signal Management
2. CIOMS VI: Management of Safety Information from Clinical Trials
3. CIOMS VIII: Practical Aspects of Signal detection in Pharmacovigilance
4. GVP module IX: Signal Management
5. Screening for adverse reactions in EudraVigilance
6. Product specific modules & guidelines
    1. GVP P1:Vaccines for prophylaxis against infectious diseases
    2. GVP P2 – Biological medicinal products
    3. GVP P3- Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

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