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Pharmacovigilance

Signal Identification and Assessment

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Objectives

- Understand what is a Signal and Safety Related Event
- Tools to detect a Signal based on post-marketing adverse event data
 - Use of qualitative and quantitative assessment methods
- Things to consider when assigning causality to an adverse event following immunization
- Evaluation once a signal is detected
- Reviewing the risk/benefit ratio for a Vaccine
- Updating the Safety Information with new adverse event information

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What is a Signal?

'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 significant likelihood to justify verification action'

Council for International Organisations of Medical Sciences (CIOMS) VIII Working Group

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What is a Signal?

- Data sources include:
 - Non-clinical studies
 - Clinical studies
 - Adverse event reports
 - Other similar vaccines

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What is a Signal?

- Based on Objective Data
- Not based on a theory or hypothesis
- Can be unexpected event or an unexpected finding to a known event
 - E.g. specificity, intensity, rate of occurrence in a population

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What is a Signal?

- Important to consider, a signal is not a confirmed finding, but is generally referred to as a hypothesis-generating situation that must be validated or disproved

Signal strengthening

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Signal Management Overview

Safety-Relevant Observation

Pharmacological Plausibility

Patient Characteristic(s) trends(s)

Related Similar Events

Class effect

Commonly Drug related event

Signal

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Signal Management

- Three Key Steps
 - Signal Detection
 - Signal Management
 - Including signal validation, signal analysis and prioritization, signal assessment, and recommendation for action
 - Update to Vaccine Safety Information

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Signal Detection

- Signal detection should use different methods approaches
 - These is no single correct way to detect signals
- **Statistical analysis or defined processes should not replace the importance of medical and scientific judgement**
- Ensure the process used is consistent and logical
- Use different data sources
 - Review of published literature
 - Review of important individual cases by Company staff
 - *Ad hoc* reports

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Safety Related Observation

- A drug event pair refers to an adverse event reported for a medicinal product
- Not all drug-event pairs are safety related observations, e.g.

Drug-Event Pair is a Safety Related Observation	Drug-Event Pair is not a Safety Related Observation
<ul style="list-style-type: none"> • Pharmacologically plausible • Event is not described in the Vaccine Prescribing Information • Vaccine related events • Several common events occurring at Vaccination site/region 	May be based on: <ul style="list-style-type: none"> • Single event in adult population • Not pharmacologically plausible • Not considered as related to Vaccine • Currently included in Vaccine Prescribing Information

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Signal Detection

- Any safety-related observation that requires further review may be considered a signal
- A safety related observation is the potential association between a medicine and an unanticipated finding which has not undergone an expert medical review

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Is the Safety Related Observation a Signal?

Safety- Relevant Observation
 Pharmacological Plausibility
 Related Similar Events
 Patient Characteristic(s) trends(s)
 Class effect
 Commonly medicine related event
Signal

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Drug Related Event and Causality

- Where a drug has been named in combination with an adverse event, an assessment of causality is needed
- Determines if a causal relationship exists between a vaccine and an adverse event
- Assessment of causality should be conducted at the completion of all investigations
 - Early assessment of causality without all information may mislead classification
- A valid diagnosis must be defined, well founded and relate to the event being assessed

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Considerations for Assessing Drug Related Event and Causality

- Which of these is not one of the five principles applied for causality assessment as specified in the WHO Aide Memoire?
 1. Consistency
 2. Strength of Association
 3. Risk-benefit balance
 4. Temporal Relationship (did the reaction occur after the vaccination?)
 5. Biological Plausibility

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Review of Adverse Events

- A valuable source of data is Company's Adverse Event (AE) Database
- AEs received should be entered into a centralized, robust, database and maintained by Pharmacovigilance/Medical personnel
- Review of AE database is a primary mode of routine post-marketing signal detection
- Evaluation of database is largely on a **qualitative** basis, however for large numbers of AEs, a **quantitative** approach may be applied

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Areas to focus on

- Serious unlisted events
- Adverse events of special interest (AESI)
- Events where if causality is associated with vaccine may significantly alter the risk:benefit ratio
- Events reports that indicate inappropriate use
- Problems associated with the vaccine administration process
- Events in special population (e.g. paediatric, elderly, pregnant or breastfeeding women, people taking immunosuppressants)

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Qualitative Adverse Event review

- Output of database review may include
 - Adverse event data review according to systematic process
 - Perform this step based on an established checklist
- Look for any trends within the data indicating a change in the number of entries occurring for a specific event
- Compare this against previous reviews to identify any change

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Quantitative Adverse Event Review

- Suggested to use for vaccines with 100 or more spontaneous AEs per year
- Uses vaccine specific information
- May include data obtained from different sources:
 - Spontaneous AE reports
 - Clinical studies
 - Published literature

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Quantitative Signal Detection Review

- Evaluate the frequency of adverse event for a product per System Organ Class (SOC) for a defined period

How does this frequency compare against existing data?

```

graph TD
    A[How does this frequency compare against existing data?] --> B[No change]
    A --> C[Higher frequency]
    B --> D[Not a signal]
    C --> E[Data suggests a new Signal]
  
```

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Disproportionality Assessment

- Disproportionality Assessment is a statistical method used to identify product-event combination at a higher frequency as compared to reference data
- Can compare against other products (inter-product analysis) or against historical data for same product (intra-product analysis)
- Different statistical algorithms have been developed for disproportionality assessments

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Disproportionality Assessment

- Simple tool used to construct data for disproportionality assessment

2x2 table of adverse event report data

	Reports for event of interest	Reports for all other events	Total
Reports for vaccine of interest	A	B	A + B
Reports for all other vaccines	C	D	C + D
Total	A + C	B + D	A + B + C + D

Adapted from CIOMS Working Group III publication

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Disproportionality Assessment

- Common statistical methods of association include

Statistic	Formula
Proportional Reporting Ratio (PPR)	$A(C + D) / C(A + B)$
Reporting Odds Ratio (ROR)	AD / CB
Relative Reporting (RR)	$A(A + B + C + D) / (A + C)(A + B)$
Information Component (IC)	$\text{Log}_2[A(A+B+C+D)/A(A+C)(A+B)]$

Adapted from CIOMS Working Group III publication

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Disproportionality Assessment

- What result indicates a change in frequency of Adverse Event?
- Example:
 - Using the Reporting Odds Ratio (ROR)
 - $\text{Ln ROR} \geq 0.45$
 - and
 - $n > 3$
- Threshold for analysis should be specified within Company procedure and justified

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SIGNAL IS DETECTED – NEXT STEPS?



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Expert Review

- Following the validation of a signal detected, an Expert Review Panel should undertake review
- Panel comprised of suitably qualified and experienced Company personnel
 - Medical Physicians/Pharmacovigilance
 - Clinical Research
 - Quality Assurance
 - Manufacturing
 - R&D/Pharmacology/Toxicology Experts
- Panel critically evaluates all data compiled as part of Signal Detection

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Expert Review and Priority Rating

- Panel should provide conclusion of assessment
 - Signal confirmed
 - Signal refuted or,
 - Request additional information
- For confirmed signals, priority rating should be assigned
 - Directs the timelines for next stage of assessment



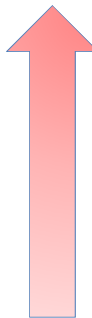
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Priority Rating

Examples:

- Priority A:** signal with potential high medical impact (e.g. fatal outcome, life threatening), change to risk:benefit assessment, or high regulatory impact
- Priority B:** serious and/or severe signal that are not Priority A
 - May include serious signals (high reporting frequency) assessed as pharmacologically plausible, high frequency of serious events specified in product labelling, AEs with potential to progress to serious condition
- Priority C:** signals with low medical impact which may not pose significant risk to subject health




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Priority Rating

- Signals with high rating should be actioned promptly
- E.g.
 - Priority A: 15 working days
 - Priority B: 60 working days
 - Priority C: 90 working days



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Impact on Risk:Benefit Ratio?

- Any signal detected and confirmed should be further assessed to determine impact on risk:benefit ratio

Does the RISK of vaccine with Product X increase based on the signal?

Does the BENEFIT of vaccination still outweigh these new risks?

Can these risks be reduced?

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Change to Risk:Benefit ratio

- Where the Signal does not impact on risk:benefit ratio, consider review of safety information provided in product label
 - Review precautions/warnings
 - Review information on possible adverse events specified in the label
 - Monitor the signal occurrence to re-validate initial conclusion
- Where the Signal does impacts on the risk:benefit ratio, Sponsor/Manufacturer should inform Health Authority
 - Assess the identified risks to determine if appropriate mitigations can be applied
 - i.e. Change in indication, exclusion of specific populations, withdrawal from supply

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Review of Risk:Benefit ratio

- Continuous evaluation of risks and benefits of vaccines is required to strengthen the confidence in immunisation programmes
 - Consider the epidemiology and natural history of a vaccine-preventable disease
 - Consider the health outcomes caused by infection against the safety risks posed by the vaccine
 - Is there an alternate option to protect the population from infection?
 - Are there steps that can be taken to reduce the risk associated with vaccination?
- Commonly, the risks associated with infection are much greater than those caused by a vaccine

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Review of Risk:Benefit ratio

- The review of a product's risk:benefit ratio may use various qualitative, semi-quantitative or quantitative methods

Adapted from CIOMS Working Group IV document

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Review of Risk:Benefit ratio

- When reviewing the ratio, all relevant data on benefits and risks should be considered, e.g.
 - Vaccine efficacy
 - Adverse event signals
- Specify all assumptions and rules used for the inclusion or exclusion of data and the judgement used when weighing the value of the data source and type
- Consider the impact of extrinsic factors or patient characteristics on the benefits and risks being considered

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Descriptive and Semi-quantitative assessment

- Benefits and risks may be described in terms of intensity (seriousness or severity) of the treated disease or adverse event, duration, and incidence in the treated population (specific for adverse events)
- Adverse events are characterized based on
 - *Seriousness*
 - *Duration*
 - *Incidence/frequency of event occurring*
- Benefits of vaccination should be considered based on the disease
 - *Seriousness*
 - *Duration (i.e. chronic, acute)*
 - *Extent of control or cure*

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Quantitative assessment

- Principles of quantitative assessment are similar to qualitative/semi-quantitative method
- Pre-defined scores are applied to each criteria to defined total score
 - Quantify vaccine efficacy
 - Define score for the severity of the AE and frequency (e.g. low=10, medium=20, high=30)

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Quantitative Assessment – Group Example

- **Please calculate the risk/benefit ratio for the following example:**
- **Benefit**
 - Hepatitis B Vaccine has been shown to illicit seroprotection in 90% of adults
- **Risks**
 - Adverse events
 - Pain at injection site (occurs in 75% of subjects, resolved within 1 day)
 - Headache (occurs in 25% of subjects, resolved within 1 day)
 - Fever, > 39°C (occurs in 12% of subjects, resolves within 3 days)
 - Neuralgia (occurs in 0.17% of subjects)

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Quantitative Assessment – Group Example

- Calculate the benefit score:
 - **Seroprotection rate x seriousness of the disease x chronicity/duration of the disease**
- Calculate the risk scores
 - Pain at injection site
 - Headache
 - Fever
 - Neuralgia
- **Frequency of AE x seriousness of event x duration**

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Quantitative Assessment

- Example provided is simple
- Assessments may include additional measures
 - Mortality Rate
 - Quality adjusted life years (QALYs) gained
 - Drug attributed lot of quality adjusted life years (DAQALYs)

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Update to Product Safety Information

- Signal evaluation may require the update to product safety information
- Company Core Safety Information (CCSI) is a valuable tool to collate the key safety information for a product
 - Commonly used as reference source for safety information to be included in Product Labelling worldwide
 - Maintained by the Manufacturer and implemented by MAH
- It is a critical outcome of a product development program
- Represents the Company position of Safety

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Product Safety Information

- Format and content of CCSI is determined by Company
 - May follow local labelling requirements
- What to include?

- Therapeutic Class	- Drug Interactions
- Indication/s	- Pregnancy/Nursing
- Dosage and Administration Instructions	- Special Populations
- Contraindications	- Adverse reactions/side effects
- Warnings and Precautions	- Overdosage

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Update to CCSI

- Product labelling to be updated to remain consistent with CCSI
- Requires notification to Regulatory Agency
 - Review local regulatory requirements
- Updates to Safety Information to be implemented in accordance with priority rating timelines
 - I.e.
 - Priority A: 15 working days
 - Priority B: 60 working days
 - Priority C: 90 working days

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Quiz question

Signal Identification process includes

- a) a process of counting and assessing adverse events as serious or non-serious
- b) determination of a possible causal relationship between an adverse event and a vaccine
- c) a process of assessing the risk of an adverse event when compared with the benefits of vaccination
- d) a systematic manner of determining the inclusion of additional safety data in the prescribing information

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Conclusions

- Signal detection is a systematic review of adverse event data to detect changes in safety profile
- There is no one single way to conduct this analysis
- Statistical or process should not override medical and scientific judgement
- Validate any possible signals by expert personnel
- If a signal is detected, re-evaluate the risk/benefit ratio to ensure the Vaccine use remains positive
- Safety Information must be updated to include new signals within a pre-defined timeframe



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System Organ Class (SOC)

- The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices
- SOC is the highest level of the MedDRA terminology, distinguished by anatomical or physiological system, disease origin and purpose.
- 26 SOC terms, e.g.
 - Cardiac disorders – heart problems
 - Renal and urinary disorders – kidney and bladder problems
 - Investigations – laboratory tests or medical investigations that gave an unusual result

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SOC terms

List available at http://www.meddra.org/sites/default/files/guidance/file/intguide_14_0_english.pdf

Blood and lymphatic system disorders	Hepatobiliary disorders	Neoplasms benign, malignant or unspecified (incl cysts or polyps)
Cardiac disorders	Immune system disorders	Pregnancy, puerperium and perinatal conditions
Congenital, familial and genetic disorders	Infections and infestations	Psychiatric disorders
Ear and labyrinth disorders	Injury, poisoning and procedural complaints	Renal and urinary disorders
Endocrine disorders	Investigations	Reproductive system and breast disorders
Eye disorders	Metabolism and nutrition disorders	Respiratory, thoracic and mediastinal disorders
Gastrointestinal disorders	Musculoskeletal and connective tissue disorders	Skin and subcutaneous tissue disorders
General disorders and administration site disorders	Nervous system disorders	Social circumstances
Surgical and medical procedures	Vascular disorders	

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