Understanding the terminology
Important definitions

- Serious
- Severe
- Adverse event following immunization (AEFI)
- Adverse event (AE)
- Adverse reaction (AR)
- Serious adverse event (SAE)
- Serious adverse reaction (SAR)
- Expected / Unexpected
- Minimum criteria for reporting to regulatory authority
- Frequency definitions

Definitions in national legislation are in general consistent (not verbatim) with ICH definitions (ICH E2A and ICH E6)
Pharmacovigilance activities
Workflow

Receipt of safety information
- Safety call center reported cases
- Clinical trial SAEs
- Spontaneous reports
- Literature and internet review

Processing of safety information
- Case reception
- Triage
- Entry into the safety database
- Data management (Query process)
- Medical review
- Case completion and cloture
- Individual case reporting

Analysis of safety information
- Aggregate analyses of safety cases and assessment of benefit/risk ratio
  - Periodic report compilation
  - Signal detection
  - Benefit/Risk assessment and mitigation

Chapalain 2014
Safety data processing
AEFI case handling workflow

Case Receipt → Safety Database → Quality Review Medical Review → Submission → Follow-up

- Case Receipt
  - Triage
  - Tracking
  - PV Notification
    - Immediate contact with reporter, if necessary

- Safety Database
  - Data entry
  - Coding
  - Narrative generation

- Quality Review Medical Review
  - Triage
  - Narrative
  - Source documents
  - Coding
  - Queries

- Submission
  - PV submission
    - All Cases
    - Expedited Reporting
    - Periodic Reporting

- Follow-up
  - Queries from PV
    - Yes
    - No
  - Case Closure
    - Integrated Narrative writing

Follow-up Received
Case Receipt

Spontaneous reports AEFI\textsubscript{s}:
- Reports from HCPs
- Reports from vaccinees
- Reports from NRA / NIP
- Literature
- Other sources

Major actions:
- Case intake / date of receipt (clock date)
- Acknowledge receipt
- Assign case number *
- Tracking of case receipt
- First check of case validity
- Request additional information, where necessary
- Translate AEFI into English, if appropriate

* depending on the PV database system (manual or electronic)
Case Triage

Major actions:
- Duplicate search
- Review of AE information:
  - Assess reported AE terms
  - Assess per regulatory guidelines / definitions:
    - Seriousness
    - Causality (relatedness)
    - Expectedness
- Case prioritization as per regulatory guidelines / regulations
- Determine regulatory clock date (initial case, follow-up information)
Seriousness assessment

- Assessment based on **outcome** of the AEFI
- ICH E2A seriousness criteria:
  - results in death
  - is life threatening
  - requires hospitalization or prolongation of hospitalization
  - results in persistent or significant disability
  - is a congenital anomaly
  - is medically important

Determines expedited regulatory reporting of AEFI
Specificities of seriousness assessment

- **Death:** only serious if event caused death
- **Hospitalization:** only serious if inpatient stay (e.g., overnight), not emergency room
- **Life-threatening / medically important (i.e., serious in the medical sense):** requires individual medical assessment
- **Company (MAH): Adverse Events of Special Interest (AESI) / designated AEFIs (MedDRA coded)**
- **CIOMS V / WHO Critical Term List (MedDRA coded)**
- **EU: Important Medical Event (IME) List (MedDRA coded)**
Relatedness (Causality)
Adverse Events following immunization AEFI

Adverse Events
All events observed after vaccination

Coincidences
Naturally occurring event not caused by the vaccine... ...but observed after vaccination

Adverse reaction
Caused by the administration of the vaccine or by the vaccine itself

• Vaccine product related reaction
• Vaccine quality defect related reaction
• Immunization error related reaction
• Immunization anxiety related reaction

AEFI (WHO/CIOMS): Adverse medical occurrence following immunization and which does not necessarily have a causal relationship with the usage of the vaccine (ICH E2A)
Methods for assessment of relatedness (causality)

**Clinical evaluation**

- Global introspection: causality inference obtained via clinical judgement, such as with an expert panel
- Most common approach for causality assessment of individual case safety report; process is known to be subjective

**Algorithm**

- Causality classes: Sets of specific questions with associated scores for calculating the likelihood of a cause-effect relationship
- Standardized instrument to assess causality in a structured way ("reliable and reproducible measurement of causality")

**Probability theory**

- Probability of a causal association calculated from available knowledge (observed versus expected)

*not useful for assessing single case reports*
Causality in vaccine safety
Main criteria

**Biological plausibility**

Examples:
- Fever after endotoxin containing vaccine
- Acute flaccid paralysis after oral polio vaccine

**Laboratory evidence of vaccine involvement**

Examples:
- Disseminated BCG in an immuno-compromised patient
- Urabe mumps vaccine in CSF of a patient with meningitis symptoms

**Evidence of increased risk after vaccination**

Examples:
- Clustering in a post vaccination period
- Higher risk in vaccinated compared to unvaccinated

**Evidence across studies**

Examples:
- Consistent increased risk of aseptic meningitis with MMR vaccines within 15-35 days post vaccination
- Consistent inability to find evidence of an association between vaccination and incidence (e.g., MMR vaccines and autism)
Components of causality assessment

**Eligibility**
Determine if information collected in AEFI case investigation is sufficient for conducting causality assessment (e.g., Brighton case definition available?)

**Data review**
Review of specific and essential information to assess causality (e.g., good case quality)

**Algorithm**
Guide in the interpretation of available data and review their consistency

**Classification**
Classify the AEFI in one of the four final WHO categories to facilitate appropriate actions (unclassifiable, consistent, indeterminate, inconsistent)
Causality Assessment
WHO Algorithm

I. Is there strong evidence for other causes?
   - Yes
     I A. Inconsistent causal association to immunization
   - No
     II. Is there a known causal association with the Vaccine/Vaccination
        - Yes
          II (Time). Was the event within the time window of increased risk?
        - No
          III. Is there a strong evidence against a causal association?
             - Yes
               III A. Inconsistent causal association to immunization
             - No
               IV Review other qualifying factors
               - Is the event classifiable?
                 - Yes
                   IV A. Consistent causal association to immunization
                 - No
                   IV D. Unclassifiable
               - No
                 IV B. Indeterminate

Mandatory Path
WHO Guideline on Causality Assessment

A. Consistent with causal association to immunization
   - A1. Vaccine product-related reaction (As per published literature)
   - A2. Vaccine quality defect-related reaction
   - A3. Immunization error-related reaction
   - A4. Immunization anxiety-related reaction

B. Indeterminate
   - B1. Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
   - B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent with causal association to immunization
   - C. Coincidental
     Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine

Unclassifiable
Specify the additional information required for classification:

*B1: This is a potential signal and maybe considered for investigation

“Unknown” “Insufficient evidence”
<table>
<thead>
<tr>
<th>I. Is there strong evidence for other causes?</th>
<th>Y N UK NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does a clinical examination or laboratory tests on the patient confirm another cause?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Is there a known causal association with the vaccine or vaccination?</th>
<th>Y N UK NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine product(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?</td>
<td></td>
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</tbody>
</table>

**Immunization error**
- Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)? |           |         |
- Was the vaccine (or any of its ingredients) administered unsterile? |           |         |
- Was the vaccine’s physical condition (e.g. color, turbidity, presence of foreign substances etc.) abnormal at the time of administration? |           |         |
- Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)? |           |         |
- Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)? |           |         |
- Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)? |           |         |

**Immunization anxiety**
- Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)? |           |         |

<table>
<thead>
<tr>
<th>II (time). If “yes” to any question in II, was the event within the time window of increased risk?</th>
<th>Y N UK NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the event occur within an appropriate time window after vaccine administration?</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Is there strong evidence against a causal association?</th>
<th>Y N UK NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there strong evidence against a causal association?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Other qualifying factors for classification</th>
<th>Y N UK NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the event occur independently of vaccination (background rate)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could the event be a manifestation of another health condition?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did a comparable event occur after a previous dose of a similar vaccine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was there exposure to a potential risk factor or toxin prior to the event?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was there acute illness prior to the event?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the event occur in the past independently of vaccination?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the patient taking any medication prior to vaccination?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there a biological plausibility that the vaccine could cause the event?</td>
<td></td>
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</tbody>
</table>

*Note: Y, Yes; N, No; UK, Unknown; NA, Not applicable.*
Expectedness in regulatory reporting

Expectedness of an AEFI depends on the Relevant Safety Information (RSI)
ICH E2A / ICHE2D

**CCSI**
- Company position / document
- Includes all relevant safety information
- Defines listedness
- Defines PSUR discussions on listedness
- Basis for labeling

**SPC / PIL**

**SPC - Summary of Product Characteristics**
**PIL - Patient Information Leaflet:**
- Medico-legal document
- Safety information approved by Regulatory Authority for health professionals and patients
- Defines expectedness
- Basis for expedited regulatory reporting

**CCSI**: Company Core Safety Information
Data entry

Major actions:
- Assign case identification number*
- Perform data entry
- Medical Coding:
  - AEFI terms
  - Medical history
  - Vaccine
- Generate narrative
- Analysis of similar events

* depending on the PV database system (manual or electronic)
Medical Coding

MedDRA® - Medical Dictionary for Regulatory Activities

Medical dictionary for all activities in the frame of Regulatory Activities

- The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation
- To standardize the communication during the whole life-cycle of a product
- Supports electronic reporting of ICSRs and eCTD
- Annual updates (version 23.0 March 2020)

Requires license

Price depends on the annual revenue of the company
Fee waiver for SMEs using EVWEB to fulfill reporting obligations in the EU
Scope of MedDRA

**IN**

- Medical conditions
- Indications
- Investigations (tests, results)
- Medical and surgical procedures
- Medical, social, family history
- Medication errors
- Product quality issues
- Device-related issues
- Pharmacogenetic terms
- Toxicologic issues
- Standardized queries

**OUT**

- Not a drug dictionary
- Medical, social, family history
- Not an equipment, device, diagnostic product dictionary
- Clinical trial study design terms
- Patient demographic terms
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
The five levels of MedDRA hierarchy

- International standardized terminology
- Enables electronic data transfer
- Data consistency of medical terms
- Multiaxiality: Anatomical, pathophysiological, etiological, functional
- High specificity on LLT level – spontaneously reported data often not specific enough
Multiaxial Structure - Example

Icterus, Jaundice neonatal, Yellow skin, Subictetric, Skin coloring yellow

Jaundice

Hemolysis

Hemolysis and related conditions

Blood and lymphatic system disorders

Cholestasis and jaundice

Hepatic and hepatobiliary disorders

Hepatobiliary disorders

Dermal and epidermal conditions

Epidermal and dermal conditions

Skin and subcutaneous tissue disorders

LLT

HLT

HLGT

SOC
Coding issues

Cascade or indirect codes
• Provide the key terms:
  • direct AE coding (e.g., dizziness) or indirect AE coding (fall and subsequent hip fracture due to dizziness)

How many codes
• Limit number of codes to understand the major issues and not get lost in lesser issues (or secondary cascade)

Lumping versus splitting
• Use diagnosis or symptoms instead of individual single events, whenever possible

Specificity
• May vary depending on case; e.g. edema may have a different medical meaning (pulmonary edema versus leg edema)

Consistency
• Many synonyms in MedDRA

Cultural, language and national differences

Points to consider
• MSSO gives tips and suggestions on coding; excellent document
Coding specificities - Examples

Medical interpretation

- Example: Reported “nausea, vomiting, diarrhea, cramps”
- LLT cramps – PT Muscle spasms - SOC Musculoskeletal and connective tissue disorders
- LLT abdominal cramps – PT abdominal pain - SOC Gastrointestinal disorders

Diagnosis versus signs and symptoms

- Example: Reported “abdominal pain, amylase and lipase elevated”
  Verbatim coding (symptoms) or pancreatitis (diagnosis)?
- Example: Reported “anaphylactic reaction with dyspnea, hypotension and laryngospasm”
  Verbatim coding diagnosis with symptoms or diagnosis and reported symptoms as co-manifestations?

Site of manifestation versus specificity

- Example: Reported “skin rash on face and neck”
  Verbatim coding of symptom only (without site of manifestation)
Data retrieval for signaling and presentation

MedDRA to retrieve and present data:

- Summary tabulations for scientific and signal detection analyses:
  - List similar events in groups to identify clusters
  - Use of SMQs (Standardized MedDRA Queries) for signal detection and monitoring
  - Present Preferred Terms PT in connection with their System Organ Class SOC
Strengths / Weaknesses of MedDRA

Strengths

• International standardized terminology
• Electronic data transfer is made easier
• Data consistency (AEFI, product information etc.)
• Multiaxiality
  • Anatomical, pathophysiological, etiological, functional

Weaknesses

• Multiaxiality
• Primary versus secondary SOCs
• Data consistency
• Weak coding system for post-marketing: high specificity on LLT level - reported data are often not specific enough

MedDRA big and complex in practice
Difficult to use in a paper-based system

MedDRA training required
Quality review

Major actions:

- Quality review (QC) 100%
- Check case for accuracy
- Check case for completeness
- Check case for consistency
- Ensure correct coding (AEFI, medical history and product)
- Check seriousness and labeling (expectedness)
Medical review

Major actions:

• Confirm triage (prioritization)
• Check case for medical sense
• Check and confirm medical coding
• Check and confirm seriousness and labeling (expectedness)
• Make company causality assessment from medical point of view and / or upgrade reporter causality
• Request non-routine follow-up, if appropriate
• Review the data for potential signals

There is no actual regulation (FDA, EMA, MHRA) that requires a physician to review ICSRs, however medically qualified personnel should review all cases.
Distribution of ICSR Reconciliation

Major actions:

• Submission of expedited report (e.g., 15 day report) according to regulatory requirements (i.e., national / global)

• Distribution to business partner as per Safety Data Exchange Agreement (SDEA)

• Distribution to Safety Monitoring Committee (SMC), if applicable

• Confirm receipt of acknowledgement

• Reconciliation with external data collection partners

• Reconciliation with product quality complaints and medical information queries
Case completion - Case closure (locking)

Major actions:

- Ensure all data are corrected
- Incorporate any request changes
- Ensure that all follow-up action are completed
- Ensure that no changes can be made after locking in the case*

* depending on the PV database system (manual or electronic)
### Vaccination Failure (Lack of Effect)

**Causes of vaccination failures**

<table>
<thead>
<tr>
<th>Type of failure</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Failure to vaccinate</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Usage-related | - Administration error (wrong route, dose, diluent)  
- Vaccination schedule not adhered to  
- Wrong storage (out of cold chain)  
- Expired vaccine used |
| Program-related | - Suboptimal recommendation (number and time points of doses - primary and booster)  
- Vaccine shortage |
| **Vaccine failure** | |
| Host-related | - Immunodeficiency, immunosuppressive therapy, health status  
- Waning immunity, age-related decrease in immune response  
- Low/Non-responders  
- Interference (antibodies or infection) |
| Vaccine-related | - Vaccine not 100% efficacious  
- Incomplete coverage of strains, variants, mutants  
- Vaccine-vaccine interactions (co-administered vaccines)  
- Manufacturing related (batch variation, quality defect) |

Vaccination Failure (Lack of Effect)
Assessment of efficacy related cases

- Efficacy-related case
  - Usage or program error?
    - Failure to vaccinate
      - HCP or well-documented
        - Non-medically qualified, insufficient information on diagnosis or tests
          - “Other” efficacy related case
            - Confirmed by appropriate test/diagnosis*
              - Confirmed vaccine failure
                - Expedited report
                  - Discuss all cases in PSUR/PBRER
            - Suspicion by HCP but not confirmed by appropriate test/diagnosis*
              - Suspected vaccine failure

* Vaccine-specific, as per internal guideline on vaccination failures


Vaccines are not 100% effective. Vaccination failure is not an event, but an assessment based on vaccine specific guidelines.
Benefits of Safety Databases

- Reporting and analytics (signal management)
- Collaboration and data sharing
- Safety functionality
- Data driven decisions
- Data standardization and data quality
Benefits of a system-based Pharmacovigilance setup

- Data entry and case handling processes automated and adapted to specific business needs and supporting all processes
- High compliance in expedited reporting and configured workflows with submission rules
- Compliant configurable PSURs and line listings
- Safety data consolidated in one system supporting all PV processes, incl. Analytics as add on systems
Typical case handling workflow of a safety database system

Data intake → Data entry → Case assignment → Case processing → QC / medical review → Submission → Archiving

Automation of PV processes can provide high quality safety data in the correct format, in context, more quickly, and with less manual effort, thereby improving timely scientific assessment.

Area dominated by the Safety database vendors:
- Oracle Safety (Argus)
- Aris Global - Aris G
Essential data for good case quality

- Reference number and description of case
- Seriousness
- Primary source of report (Reporter)
- Patient information: identifier, age at onset, sex, medical history, risk factors
- Adverse event
- Outcome
- Vaccine: brand name or generic and indication
- Vaccine information: route and date of administration, # of doses, batch #
- Concomitant medication
- Action taken
- Time to onset
- Causality assessment
- Case narrative
- Assessment of missing information

4 minimal requirements