ICSR* / AEFI Receipt, Handling, Follow-up and Reconciliation

*ICSR: Individual Case Safety Report

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Pharmacovigilance activities Workflow

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

Processing of safety information:
- Case reception
- Triage
- Entry into the safety database
- Data management (Case process)
- Medical review
- Case completion and closure

Analysis of safety information:
- Individual case reporting
- Aggregate data review
- Aggregate analyses of safety cases and assessment of benefit/risk ratio
- Periodic report completion
- 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
  - Case generation and 100% QC

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

Submission:
- All Cases
  - PV submission
  - Triage
  - Narrative
  - Source documents
  - Coding
  - Queries
  - PV submission

Follow-up:
- Queries from PV
  - Yes
    - Periodic Reporting
    - Expedited Reporting
  - No
    - Queries Issued
    - Case Closure
      - Integrated Narrative writing

Follow-up Received
Case Receipt

Spontaneous reports AEFIs:
- 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**)
### Components of causality assessment

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>Determine if information collected in AEFI case investigation is sufficient for conducting causality assessment (e.g., Brighton case definition available?)</td>
</tr>
<tr>
<td><strong>Data review</strong></td>
<td>Review of specific and essential information to assess causality (e.g., good case quality)</td>
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<tr>
<td><strong>Algorithm</strong></td>
<td>Guide in the interpretation of available data and review their consistency</td>
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<tr>
<td><strong>Classification</strong></td>
<td>Classify the AEFI in one of the four final WHO categories to facilitate appropriate actions (unclassifiable, consistent, indeterminate, inconsistent)</td>
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Causality Assessment
WHO Algorithm

The first step in causality assessment is to establish a firm diagnosis of the AEFI using accepted clinical case definitions (i.e. Brighton case definitions)
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

"Unknown" "Insufficient evidence"

Unclassifiable
Specify the additional information required for classification:

*B1: This is a potential signal and maybe considered for investigation
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 24.0 March 2021)

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

![Diagram of Reconciliation Process]

- Reconciliation Partner
  - Group Company
  - Distributor

- Initial AEFI Listing

- PV Department
  - Comparison of reported AEFI cases performed by PV Department

- Finalized AEFI Listing

- Data query:
  - yes
  - Discrepancies
  - no

- Completion of reconciliation

<table>
<thead>
<tr>
<th>Parameter/variable</th>
<th>Requirement</th>
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<tbody>
<tr>
<td>PV Manufacturing Company Number (MCN)</td>
<td>exact match, if applicable</td>
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<tr>
<td>Other Reference No.</td>
<td>exact match</td>
</tr>
<tr>
<td>Product name</td>
<td>exact match</td>
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<tr>
<td>Country of report</td>
<td>exact match</td>
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<tr>
<td>Primary source</td>
<td>exact match</td>
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<tr>
<td>Patient information</td>
<td>exact match</td>
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<tr>
<td>Type of report</td>
<td>exact match</td>
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<tr>
<td>Receipt date</td>
<td>exact match</td>
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<tr>
<td>Batch No.</td>
<td>exact match</td>
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<td>Reported term</td>
<td>plausible/consistent</td>
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Example of AEFI listing for reconciliation

<table>
<thead>
<tr>
<th>Internal Reference Number</th>
<th>Country</th>
<th>Patient age</th>
<th>Patient sex</th>
<th>Product Name</th>
<th>Batch number</th>
<th>Reported Term</th>
<th>Date received</th>
<th>Initial/ Follow-up/ Duplicate</th>
<th>Date sent to PV</th>
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DCVMN PV Training July 2021 Hartmann
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)
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.
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
THANK YOU

Questions?