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Handling and Processing Safety Reports from Clinical Trials and Spontaneous Origin

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- Individual case safety reports (ICSRs) and the Serious adverse event (SAE) reporting is most commonly associated with Pharmacovigilance (PV).

- Adverse event (AE) reporting consumes a significant amount of resources for drug regulatory authorities and drug safety departments in pharmaceutical companies.

- AE reporting starts as soon the new drug molecule is introduced to the humans during clinical trials.

- Adverse event (AE) reporting involves the receipt, triage, data entering, assessment, distribution, reporting, and archiving of AE data and documentation.
Collection, processing and submission of safety reports

**RECEIPT**
- Case Input
  - Safety Call Center Reported Cases
  - Clinical Trial SAEs
  - Spontaneous Reports
  - Literature Search Cases

**TRIAGE, DATA ENTERING, ASSESSMENT**
- Medical Input / Review / Final Triage
- Safety Data Processing
  - Triage
  - Data Entry
  - Query Process
  - QC
  - Case Closure
- Safety Systems Support

**DISTRIBUTION, REPORTING**
- Case Output
- Aggregate Output
- Output Analysis
  - Periodic Report Compilation
  - Signal Analysis
  - Benefit-Risk Assessment and Mitigation
Step 1: Case Input or AE collection

- It involves collection of adverse experience information from multiple sources.
- Traditional sources are **clinical trials** and **spontaneous reports**
- Other sources of information include:
  - Solicited reports from patient support programs
  - Surveys
  - Epidemiological studies
  - Post marketing studies (PMS)
  - Disease registries
  - Drug Regulatory Authorities and other database
  - Licensor
  - Media (including social media and websites)
Step 2: Case Triage or Case assessment

- Complaint is receive at the PV department and is classified for processing.

- **Activity 1:**
  Reports is date stamped when received (generally should be done within 24 hours of receipt).

- **Activity 2:**
  Initial triage is performed by DSAs to determine whether the report needs urgent processing (SUSARs, high priority reports).

- **Activity 3:**
  Triage also covers validation of case report for accuracy, completeness and bonafied information as per regulatory requirements i.e:
  - Identifiable patient
  - Identifiable reporter
  - Suspected drug
  - Adverse drug reaction/Product quality complaint.

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Collection ➔ Triage ➔ Booking ➔ Processing ➔ Medical Evaluation ➔ QC & submission

The "4 Elements" of an AE case

- Identifiable patient
- Identifiable reporter
- Suspected drug
- Adverse drug reaction/Product quality complaint.
Step 3: Case booking and processing

- Following triage, the **case information is entered into a computerized safety database**.

- Drug safety database (Aris G, Argus, etc) is designed to collect safety data in an organized manner.

- Various **mandatory fields** are filled by the data entry personnel e.g. date of receipt of ADR, patient, reporter, AE, suspected drug, seriousness criteria and reporter causality assessment.

- Other required information as per local regulations include: type of source (spontaneous, literature, clinical trial) and **duplicate check**.

- Once minimum information is entered for reporting, the case is saved and assigned a **manufacturer control number** (MCN).
Step 3: Case booking (Spontaneous cases)

- Low stringent conditions are considered to accurately perform a duplicate check.
- If no duplicate is found then the case is booked and a unique MCN is generated.
Step 3: Case booking (Clinical Trial)

- Drug
- AE
- Patient initials
- Reporter
- **Study details (type and number)**

- Low stringent conditions are considered to accurately perform a duplicate check.
- If no duplicate is found then the case is booked and a unique **MCN** is generated.
Additional information is added during case initiation

<table>
<thead>
<tr>
<th>Report</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grouped</td>
<td></td>
</tr>
<tr>
<td>Priority</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>Report Type</td>
<td>ADVERSE EVENT</td>
</tr>
<tr>
<td>Report Origin</td>
<td>STUDY</td>
</tr>
<tr>
<td>Classification</td>
<td>NEW INFO-SUBSTANTIVE</td>
</tr>
<tr>
<td>Maternal Flag</td>
<td></td>
</tr>
<tr>
<td>Medically Confirmed</td>
<td>YES</td>
</tr>
<tr>
<td>Licensee Case</td>
<td>YES</td>
</tr>
<tr>
<td>Date at Company</td>
<td>8</td>
</tr>
<tr>
<td>Date at Collection Site</td>
<td></td>
</tr>
<tr>
<td>Date at Proc. Centre</td>
<td>15</td>
</tr>
</tbody>
</table>

Collection ➔ Triage ➔ Booking ➔ Processing ➔ Medical Evaluation ➔ QC & submission
Case processing by DSA/ PV scientist

- DSA add all the information reported in the ADR Reporting form (CIOMS Form/ MedWatch Form)

- Other activities include entering the following information on drug safety data base:
  - Narrative writing
  - Findings of laboratory investigation
  - Company causality assessment
  - and labeling of ADR (USPI, CDS, IB, Local document)
  - Query for more information or if any discrepancy
  - Data review/validation
- **Case priority**: Immediate/High/Medium/Low (can be changed).
- **Report Origin**: Study/ spontaneous
- **Classification**: New info substantive/ non-substantive, data correction substantive/ non-substantive
- **Medically confirmed**: All study case or Health Authority (medically confirmed), spontaneous case (depends on reporter)
1) Report Screen (Cont..)

- **Summary Case, Legal Case:** left blank (but can be changed).
- **Event Country:** when country where event occurred and where it was reported are different.
- **External case ID:** Case ID from other reference.
- **Authority number:** Unique number assigned by Health Authority (reports from HA)
- **Design:** Blind/ single blind/ open/ double blind/ triple blind/ unknown (can be changed).
- **Phase:** I/II/III/IV
1. **Study Type**: CTC, CT-NC, Compassionate use, Drug surveillance (PMS studies)
2. **Study**: unique study ID (usually $ or % used to search appropriate study).
   - On correct study selection: Study name and investigator auto filled.
3. **EUDRACT**: Authorization number if study has a trial conducted in EU.
4. **Design**: Blind/ single blind/ open/ double blind/ triple blind/ unknown (can be changed).
5. **Phase**: I/II/III/IV
2) Patient Screen

<table>
<thead>
<tr>
<th>Patient Info. at First AE Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initials</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Birth Date</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
</tr>
<tr>
<td><strong>Calculated Age</strong></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
</tr>
<tr>
<td><strong>Height</strong></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
</tr>
<tr>
<td><strong>Maternal Flag</strong></td>
</tr>
<tr>
<td><strong>Pregnancy Related</strong></td>
</tr>
<tr>
<td><strong>Patient Postal Code</strong></td>
</tr>
</tbody>
</table>

- **Initials of first, middle and last name**
- **M/F/unknown**
- **partial DOB (year, or month and year and tick**
- **autopopulated using date of first AE and DOB (if both are entered)**
- **Other:**
  - free text: Hispanic/Black/ Asian

**AE related to baby/ foetus/ placenta/ umbilical cord/ amniotic fluid**

**AE related to mother**
(disabled if pregnancy is flagged in the initiate/report screen)
3) Reporter Details

- **Primary reporter**
  Reporter most likely to have access to detailed information regarding drug experience e.g. 1) patient reported event and a follow-up report is received from a doctor (doctor primary reporter).
  
  2) nurse phones on behalf of doctor (enter the name of the doctor).
  
  3) if **more than one doctor provide information** on an event, the doctor who treated the event (or if the latter has not provided the information then the doctor who proscribed the drug

- **Primary reporter must be first in the list of the reporters** (Resequence buttons should be used if necessary)
Not qualified health professionals:
Student doctor, student dentists, student vets

Type: Licensee/ Consumer/ HP/ Literature/ Pharma company/ Reg Auth/ Unknown/ Other

Occupation: Doctor of medicine/ dental sciences, non-HP, Nurse, other-HP, Pharmacist, unknown

For Literature cases:

Author’s name

Name of journal, Year, Volume, Number, Page
3) Drugs Details

- Information pertaining to **Suspect drug/ Concomitant drug/ Past drug**.
- Suspect drug should be the primary drug.
- Drug name selected from WHO Drug Dictionary.
- Appropriate flag should be selected.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary</th>
<th>Pregnancy</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>SUSPECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unblinded</td>
<td>Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Medication</td>
<td>Generic Name</td>
<td>Primary Suspect Drug from WHO Drug Dictionary</td>
<td>Autopopulated once Trade name is entered</td>
</tr>
<tr>
<td>Reg Status</td>
<td>US</td>
<td>AUS</td>
<td></td>
</tr>
<tr>
<td>Prim Rptr Ctry</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Indication Terms**
  - Reported
  - MedDRA LLT
  - MedDRA - Pr

- **Flags**
  - Lack of Drug Effect
  - Technical Complaint
  - Drug Interaction
  - Drug Overdose
  - Drug Dependence
  - Drug Abuse
  - No Flags Required

- **Dosage**
  - Route
  - Form

- **Study**: IND number
- **Spontaneous**: NDA

- **Normal scenario**

- **Product Counterfeit**

- Drug indication enter as reported or “Drug use for unknown indication”.
3) Drugs THERAPY Details

- If the drug flag is marked as Technical complaint/Product Counterfeit

Dose Format: DETAILED DOSING INFO

**Dates**

- Start Date
- Stop Date
- Therapy Ongoing: UNKNOWN

**Duration**

- Reported
- Calculated

**Dosing Levels**

- Dosing Amt: 80 mg
- Dosing Freq: 1 per 1 day (OD/BID/QID)
- TDD: 80 mg

- Allow Ranges

**Text**

- At night

- if stop date is not provided: continued, unknown, N/a (suicide/death cases)

- if only total duration of intake is provided: no start/stop date reported.
### 3) Drugs THERAPY Details (during pregnancy)

- **Mother/Father (who consumed medicine)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary</th>
<th>Pregnancy</th>
<th>Reactions</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SUSPECT</td>
</tr>
</tbody>
</table>

- **Exposure Time Period**
  - Before Conception
  - In Trimester 1
  - In Trimester 2
  - In Trimester 3
  - At Delivery

- **Interval Between Last Drug Exposure and Conception**
  - Reported
  - Calculated
  - Last Therapy
  - Stop Dt
  - Conception Dt

- **Parent Exposed**
4) Adverse Event Details

- **Report event as reported** (should not be change by self).
- **Link Reported term with appropriate LL/PT** (using MedDRA).
- Flag seriousness criteria as reported (for serious cases)
- Seriousness criteria flag can be changed (for non-serious/low cases)

<table>
<thead>
<tr>
<th>Terms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Type</td>
<td>REPORTED</td>
</tr>
<tr>
<td>Reported</td>
<td>Chest pain</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Low Level</td>
<td>Angina</td>
</tr>
<tr>
<td>Preferred</td>
<td>Cardiac XXXXXX</td>
</tr>
<tr>
<td>High Level</td>
<td>XXXXXX</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>XXXXXX</td>
</tr>
</tbody>
</table>

**Applicable Seriousness Criteria**
- CONGENITAL ANOMALY
- DEATH
- DISABILITY
- INSUFFICIENT INFORMATION
- INTERVENTION REQUIRED
- LIFE-THREATENING
- MEDICALLY SIGNIFICANT
- NEW/PROLONGED HOSPITAL
- NON-SERIOUS
- OVERDOSE
<table>
<thead>
<tr>
<th>FDA Designated Medical Events (DME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still birth</td>
</tr>
<tr>
<td>Torsades de pointes</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Steven-Johnson syndrome</td>
</tr>
<tr>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Abortion</td>
</tr>
<tr>
<td>Malignant hypertension</td>
</tr>
<tr>
<td>Status epilepticus necrolysis</td>
</tr>
<tr>
<td>Diffuse intravascular coagulation (DIC)</td>
</tr>
<tr>
<td>Acute liver failure</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
</tr>
</tbody>
</table>

- List is short & provides only example of type of event generally **be considered potentially medically important** (i.e. medically significant event).
- Careful consideration should be done in **upgrading the AE**.
- **Event outcome:**
  - Improved
  - Resolved
  - Resolved with squealae
  - Worsened
  - Unknown
  - Not provided
  - N/A (Death/ Pregnancy)

<table>
<thead>
<tr>
<th>Terms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Type</td>
<td>REPORTED</td>
</tr>
<tr>
<td>Reported</td>
<td></td>
</tr>
<tr>
<td>Event Outcome</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td></td>
</tr>
<tr>
<td>Reporter Highlighted</td>
<td></td>
</tr>
<tr>
<td>Onset Date</td>
<td></td>
</tr>
<tr>
<td>Resolved/Improved Date</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td></td>
</tr>
</tbody>
</table>

*Mild/moderate/severe (if reported in event description)*
5&6) Medical History & Lab investigations

- Medical history and lab investigations should be in chronology.
- Most relevant MH and Lab investigation should be at the top.
- Normal Lab investigation could be added from a reference book (if not reported but important).
- Error in its entry result in non-substantive error.

<table>
<thead>
<tr>
<th>Test/Procedure Name</th>
<th>FIBRINOGEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test/Procedure Date</td>
<td>26 JUN 2008</td>
</tr>
<tr>
<td>Result</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>150.0000</td>
</tr>
<tr>
<td>Result Low</td>
<td>600.0000</td>
</tr>
<tr>
<td>Result High</td>
<td></td>
</tr>
<tr>
<td>Unit of Measure</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Additional Info</td>
<td></td>
</tr>
</tbody>
</table>

All Lab Test Procedures for this Report - Sorted by Sequence (A)

<table>
<thead>
<tr>
<th>Seq (A)</th>
<th>Test/Procedure Name</th>
<th>Lab Test Date</th>
<th>Result (Low)</th>
<th>Result (High)</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FIBRINOGEN</td>
<td>26 JUN 2008</td>
<td>852.0000</td>
<td></td>
<td>MG/DL</td>
</tr>
<tr>
<td>2</td>
<td>GLUCOSE</td>
<td>26 JUN 2008</td>
<td>321.0000</td>
<td></td>
<td>MG/DL</td>
</tr>
<tr>
<td>3</td>
<td>UREA</td>
<td>26 JUN 2008</td>
<td>74.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8) Narrative

Spontaneous Cases
- Narrative usually consists of 4 paragraphs
  - Introduction
  - Medical history & concomitant drugs
  - Main body
  - Causality & follow-up information

E.g. This spontaneous case received on DD/MM/YY via Reg Authority, was reported by a physician and concerns a 32 year old female (BMI) who experiences life threatening event of cerebral hemorrhage while taking XXXX for (drug indication).

The patient’s medical history included ........ and was taking ......concomitant (only relevant MH & concomitant medication)

On DD/MM/YY, the patient started receiving oral paracetamol (200 mg tablet) at a dose of 200 mg thrice daily. Three days later, she experience high grade fever. The same day, lab test r

Study Reports

This clinical case was receive on DD/MM/YY and concerns a 52 year old female (CRTN) who was enrolled in the study “title” and developed pancytopenia.
8) Drug Event relationship

- Association b/w drug and event is established.
- Response of AE to Dechallenge and rechallenge.
- **Causality** (i.e. drug event relationship is established).
- **Labeling** as per expectedness of AE in reference safety information document.
- **SUSAR** (reported causality is related while the AE is unexpected in company ref doc.
- SUSARs qualify for expedited reporting (triage should be done carefully).
- **Reporter causality** capture as reported, however **company causality** is assessed by performing (Single case assessment).
Single case assessment (SCA) for Serious Spontaneous reports

- Single case assessment is done to determine the Company drug/event relationship (i.e. expectedness).
- It consists of a set of 10 questions, which provide numerical output indicating the strength of association b/w the drug and AE.
- Scoring is based upon the amount and relevance of information that is available.
- It serves as a guideline for assigning the causality into 4 broad categories (definite, probable, possible and unlikely).

<table>
<thead>
<tr>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Are there previous conclusive report in this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2) Did AE appear after the suspect drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>3) Did the AE improved when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4) Did the AE reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>5) Are there alternative causes that could on their own cause AE?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>6) Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>7) Was the drug detected in blood (fluid) in conc known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8) Was the reaction more severe on dose increase or vice versa?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9) Did the patient had similar reaction to the similar drugs previously?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10) Was the AE confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Interpreting the Naranjo Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Causality</th>
<th>Reporter drug relationship</th>
<th>Company Drug relationship</th>
<th>Drug Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>9+</td>
<td>Definite</td>
<td>N/Y/UNK</td>
<td>Y</td>
<td>Related</td>
</tr>
<tr>
<td>5-8</td>
<td>Probable</td>
<td>N/Y/UNK</td>
<td>Y</td>
<td>Related</td>
</tr>
<tr>
<td>1-4</td>
<td>Possible</td>
<td>Y/UNK</td>
<td>Y/UNK</td>
<td>Related</td>
</tr>
<tr>
<td>0 or less</td>
<td>Unlikely</td>
<td>N</td>
<td>N</td>
<td>Unrelated</td>
</tr>
</tbody>
</table>
Medical evaluation

In medical evaluation, the HCP or DSP checks the:

- Appropriate linkage of reporter AE with the preferred term.
- The labeling of the AE against the reported events in the company labeling documents.
- Seriousness and causality assessment.
- Alternative cause of the ADR and CIOMS comments (if any).
- Medical history and additional information needed.
- Narrative (completeness, chronology and medical relevance).
Query or Additional Information

- Additional information is requested from the affiliate or the investigator for any discrepancy or support case information.
- Query can be sent during case processing and medical review (i.e. ideally when the case is open)
- SOPs on query process.
Quality Check

- ICSRs are **randomly selected** for quality check.
- Ideally QC is done, when the ICSR/SAE report is ready for submission to the regulatory authority.
- Only important fields (which could lead to substantive correction) are checked against the source documents.
- Case after satisfactory QC is locked/closed and submitted to regulatory department and to licensee.

<table>
<thead>
<tr>
<th>REPORT SCREEN</th>
<th>1</th>
<th>Report Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Classification</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Local/External case ID</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Date received at company</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Medically confirmed</td>
<td></td>
</tr>
<tr>
<td>PATIENT SCREEN</td>
<td>6</td>
<td>Patient initials</td>
</tr>
<tr>
<td>7</td>
<td>Patient gender</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Birth date / Age at time of Event</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Age Group</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Date of death if fatal outcome</td>
<td></td>
</tr>
<tr>
<td>REPORTER SCREEN</td>
<td>11</td>
<td>Last name/organisation</td>
</tr>
<tr>
<td>12</td>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Reg/Patient reference ID</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Reporter Type</td>
<td></td>
</tr>
<tr>
<td>SUSPECT ROCHE DRUG/COMPARATOR AND DRUG THERAPY</td>
<td>15</td>
<td>Drug selection/correct IND/NDA/formulation</td>
</tr>
<tr>
<td>16</td>
<td>Dose, Frequency, Route and Therapy dates</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Lot number (if provided)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Flags</td>
<td></td>
</tr>
<tr>
<td>CONCOMITANT MEDICATIONS</td>
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<td>Drug names and therapy information</td>
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<tr>
<td>TEXT/NARRATIVE</td>
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<td>Full narrative</td>
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<tr>
<td>ADVERSE EVENT SCREEN</td>
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<td>Reported term</td>
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<td>22</td>
<td>Seriousness criteria</td>
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<td>23</td>
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<td>DRUG/EVENT SCREEN FOR SUSPECT AND COMPARATOR DRUGS</td>
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<td>All relevant labels entered and correct</td>
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<td>25</td>
<td>Causality (Except for legal cases)</td>
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</tbody>
</table>
TYPES OF REPORTS RECEIVED AT THE PV CENTER:

- Spontaneous Serious/Non-serious case reports or SAE from clinical trials:
  - Death
  - Lack of Effect (LOE)
  - Drug exposure during Pregnancy
  - Drug Counterfeit
  - Drug Interaction
  - Drug Dependence
  - Drug Overdose
  - Suicide
  - Drug Abuse
  - Medication Error (storage, prescribing, dispensing, administering)
**Expedited Reporting**

- ICSRs that involve a **serious and unlabelled event** (an event not described in the drug's labeling) that is **considered related to the use of the drug**.

- (Spontaneous reports are typically considered to have a positive causality, whereas a clinical trial case will typically be assessed for causality by the clinical trial investigator and/or the license holder.)

- In most countries, the **timeframe for reporting expedited cases** is **15 calendar days** from the time a drug company receives notification (referred to as "Day 0") of such a case.

- **Within clinical trials** such a cases is referred to as a **SUSAR** (a Suspected Unexpected Serious Adverse Reaction).

- If the **SUSAR involves an event that is life-threatening or fatal**, it may be subject to a **7-day "clock"**. Cases that do not involve a serious, unlabelled event may be subject to non-expedited or periodic reporting.
**Signal Detection**

- The WHO defines a safety signal as: “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”.

- Usually **more than a single report is required to generate a signal**, depending upon the event and quality of the information available.

- **Data mining pharmacovigilance databases** is one approach that has become increasingly popular with the availability of extensive data sources and inexpensive computing resources.

- The data sources (databases) may be owned by a pharmaceutical company, a drug regulatory authority, or a large healthcare provider.

- Individual Case Safety Reports (**ICSRs**) in these databases are retrieved and converted into structured format, and **statistical methods** (usually a mathematical algorithm) are applied to calculate statistical measures of association.
Signal Detection (cont..)

- If the **statistical measure crosses an arbitrarily set threshold**, a signal is declared for a given drug associated with a given adverse event.

- All signals deemed worthy of investigation, require further analysis using all available data in an attempt to confirm or refute the signal.

- If the **analysis is inconclusive**, additional data may be needed such as a post-marketing observational trial.

- Ideally, the goal of SD is to identify ADRs that were previously considered unexpected and to be able to provide guidance in the product's labeling.

  *(as to how to minimize the risk of using the drug in a given patient population).*
The Goal of AE reporting

When a drug is marketed it may be used in patient populations that were not:

- Studied during clinical trials (children, the elderly, pregnant women, patients with co-morbidities not found in the clinical trial population, etc.)

- A different set of warnings, precautions or contraindications (where the drug should not be used at all) for the product's labeling may be necessary in order to maintain a positive risk/benefit profile in all known populations using the drug.
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