Fundamentals of an Effective PV system

Objectives

- What data should be collected
- How should data be recorded
- Follow up on adverse event outcomes
- Effective analysis of adverse event data

What are the aims of Pharmacovigilance System?

- Improve patient care and safety in relation to the use of medicines and all medical interventions
- Improve public health and safety in relation to the use of medicines
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and
- promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public

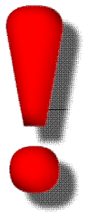
Effective communications in Pharmacovigilance. *The Erice Report. International Conference on Developing Effective Communications in Pharmacovigilance*, Erice, Sicily, 24-27 September 1997, at which a policy statement was drawn up known as The Erice Declaration.

How are these aims achieved?

- Collecting information useful in the surveillance of products
- Implementing systems to capture data from various sources
  - Clinical trials
  - Registries
  - National Immunization Programmes
  - Surveys of healthcare providers
  - Licensed partners
  - Medical and scientific literature
- These data are scientifically and systematically reviewed and actions based on the outcomes implemented

Who should report AEs to Company PV Staff

- Events received by **anyone** within Company should be reported to PV staff
  - Sales
  - Medical
  - Quality Assurance
  - Manufacturing
  - Management
  - Everyone!



Training of Company Staff is important to ensure awareness of Pharmacovigilance

Receipt of Adverse Event

- Once initial information on event is received, it should undergo preliminary review and assigned a priority rating
  - A Case Manager may be assigned to collect information and follow up case information
  - Initial review should determine if report is valid or not valid
- Confirm all the relevant information is included
- Important to assign an identification number
  - Unique number that can assist with traceability
- **Review previous reports to confirm event is not duplicated**

Receipt of Adverse Event

The day the initial report of event is received = Day 0

Recall of Definitions

- Adverse Event (AE):
  - An AE is any untoward medical occurrence in a patient, consumer or a clinical investigation subject administered a medicine, which does not necessarily have to have a causal relationship with this treatment.
- Adverse Reaction (AR):
  - Concern noxious or unintended response to a medicine
  - Includes ARs that arise from
    - the use of a medicine within the terms of the marketing authorisation;
    - the use outside the terms of the marketing authorisation, including overdose, abuse, off-label use, misuse, and medication errors; or
    - occupational exposure

The phrase 'responses to a medicine' means that a causal relationship between a medicine and an AE is at least a reasonable possibility

Excerpt from *Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines*

Definitions

- **Serious AR** is any untoward medical occurrence that at any dose:
  - results in death;
  - is life-threatening
  - requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
  - results in persistent or significant disability/incapacity;
  - is a congenital anomaly/birth defect; or
  - is a medically important event or reaction.
- *Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious*

Excerpt from *Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines*

Recording of Adverse Event Data

- Data from Individual Case Safety Report (ICSR) should be entered into a centralized database
- Database may be based on simple tools e.g. Spreadsheet
- More sophisticated database systems are available
  - May require specialist training and validation as part of implementation
- Choose a system that best suits your Company's requirements

Please share any information on the systems used within your Company to record Safety Data

Recording of Adverse Event

- Data from case report should be entered into database within pre-defined timeframe:
  - E.g. enter within 24 hours of receipt
- Ensure Minimum Information for report is included:
  - An identifiable patient
  - One or more identifiable reporter(s)
  - One or more suspected reaction(s); and
  - One or more suspected medicine(s)
- Without minimum information such as this, case should not be considered valid

Recording of Adverse Event

- Along with minimum information required, attempt to record the following
  - Lot/batch number
  - Patient demographics
    - Age, gender, weight, date of birth, etc
  - Country/city where event occurred
  - Concomitant Medications
  - Any additional important medical information
- If reporter is patient, seek permission to contact their healthcare professional
- Is report is healthcare professional, seek consent to follow up case

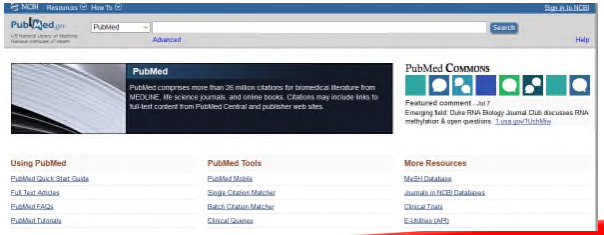
Recording of Adverse Event

- For reports received from Healthcare Professionals, obtain initial assessment of causality
  - Was this event associated with the Vaccine administered?
- 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

Recording of Adverse Event from Literature Sources

- Adverse events identified through literature search should be managed in the same way as other events
- Follow up may be required with the author/s to gain further information to allow assessment of case



Recording of Adverse Events

- Recording of events into pre-defined forms assists with capturing information
  - CIOMS form *Suspect Adverse Reaction Report* is commonly applied

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

Recording of Adverse Events

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Recording of Adverse Events

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Content of the CIOMS Form will assist in developing Safety Database

Recording of Adverse Events

- Data source should be noted and filed with all case documentation
  - If received via email, save the email
  - If received via phone call, prepare call record summarizing the reporter, date, time, who received the call and a summary of the conversation
  - If received in person, prepare a meeting record

Case Evaluation

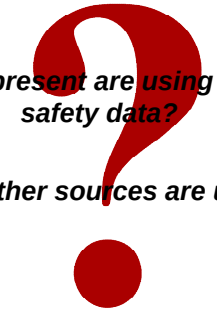
- A medical evaluation should be conducted for:
  - All serious cases, from all sources
  - Non-serious cases for interventional company-sponsored clinical trials
  - Follow up information for non-serious ICSR that were assessed as serious by medical assessor
  - Follow up of information specifically requested by medical assessor
- Medical evaluation should be completed within a defined timeframe
- Medical evaluation should also **code** the event terms

Coding of Medical Terms

- For safety databases, adverse events, diagnoses, indication, laboratory tests, death causes, diseases, surgical procedures should be coded
- Ensure consistency in naming of terms
- MedDRA (Medical Dictionary for Regulatory Activities) is commonly used source
- Differing terminology at different stages of development impacts ability to cross reference and analyse data

Visit: www.meddra.org

Coding of Medical Terms



How many Companies present are using MedDRA for coding of safety data?

What other sources are used?

MedDRA

MedDRA is an extensive medical terminology with a unique architecture and features that support public health monitoring, data analysis, communication (both electronic and traditional) and data management. This terminology is hierarchical, multiaxial, multilingual, regularly-updated, and strictly maintained. Since it has been in widespread use for more than a decade, it is stable and mature with extensive supporting materials

Excerpt from MedDRA website

Coding of Medical Terms

- When coding of terms, always select a lowest level term (LLT)
- Accurately choose the term that reflects the reported verbatim information
- Include the Preferred term in case information

Example:

Reported term	Lowest Level Term	Preferred Term
Pain in head	Pain head	Headache
Migraineous headache	Migraine headache	Migraine
Headache after surgery	Headache postoperative	Procedural Headache

Coding of Medical Terms

- When one specific term is not sufficient, it may be appropriate to select multiple terms
- If changing to preferred term alters the meaning, include ‘As Reported’

Reported	Term entered ‘As reported’	LLLT
Pain in head and neck	Pain in head	Pain Head
	Pain in neck	Pain Neck

- Select the term for each AE reported, regardless of causality association

Case Follow up

- Following receipt of initial report, objective is to collect as much relevant information as possible
- This will include an initial assessment of causality
- Where data within the ICSR is outstanding or the resolution of the AE is unknown, follow up with the reporter maybe required
- Determine most effective method to obtain further information
- Record all contact with the reporter for traceability
  - If contacted by phone, prepare record of conversation
  - If contacted by email, save all correspondence with case records
- Follow up process should document minimum number of contact attempts made to gain further information

Follow up Investigations

- For some events or groups of events, completion of medical review of case is not sufficient
- Investigations should involve multiple approaches
  - Clinical history of patient group
  - Effectiveness of Vaccination program and its delivery
  - Possible quality related issues
- Involvement of experts from different disciplines will provide additional scientific insights into possible wider issues

This will be covered be the Interactive Session

Evaluation of Adverse Event Database

- Through the use of common terminology, analysis of events through grouping of terms can be achieved
- Periodic review of known adverse events can provide early indication of signal

Overview

- Quality of recorded data will determine the ability to gain further understanding of product safety
- Data should be as complete as possible to ensure all critical information is gathered
- Proactively follow up of case to gather outstanding information
- Coding of data ensures **clear**, **consistent** terminology