Pharmacovigilance Methods and Post-Authorisation Safety Studies

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Objectives

At the end of this module participants would be expected to:

– Know the various methods used in pharmacovigilance
– Know the various approaches used for post-authorisation safety studies
– Be able to distinguish between interventional and non-interventional studies
– Appreciate the importance of additional studies to address safety concerns
From the PV Toolkit
www.pvtoolkit.org

PV Toolkit Contents

- About PV Toolkit
- Introduction
- Functions of National PV System
- How to Setup a PV Center
- The WHO Programme for international Drug Monitoring and how to join

PV Methods
- Definitions and Terminologies
- Relationship/causality assessment
- Signal identification General Approach

More on this Topic
- Passive Surveillance
- Stimulated Reporting
- Active Surveillance
- Targeted Clinical Investigations
- Descriptive Studies

Signal methods can be used to collect safety information in pharmacovigilance. In all national pharmacovigilance systems, SPONTANEOUS REPORTING forms the bedrock of the system despite its well-known limitation of under-reporting. It is relatively inexpensive and provides a life-time monitoring of all medicines in all patients in any healthcare system. There are other systems including active patient follow-up e.g. Cohort Event Monitoring (CEM). Brief highlights of the various pharmacovigilance methods are given below (adapted from the ICH E2E Guidelines. The full document can be downloaded from the ICH website using this link.

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Pharmacovigilance Methods

• Spontaneous reporting is the mainstay of pharmacovigilance

• Definition: Spontaneous report, synonym: Spontaneous notification
  – An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme
Spontaneous vs Stimulated Reporting

• Stimulated reporting can occur in certain situations, such as after a direct healthcare professional communication, a publication in the press, or questioning by company representatives, and adverse reaction reports arising from these situations are considered spontaneous reports.

• Reporting can also be stimulated by invitation from patients’ or consumers’ organisations to their members.

• Reporting made in the context of early post-marketing phase vigilance (EPPV), e.g. in Japan, is also considered stimulated reporting.
Pharmacovigilance Methods

- These form part of the ICH E2E guidelines
- ICH E2E guidelines specify which methods and approaches could be adopted
- The EU regulations are much clearer and more specific on PASS
  - Most recommended PASS are more or less embedded in the ICH E2E guidelines
E2E Annex – Pharmacovigilance Methods

1. Passive Surveillance
2. Stimulated Reporting
3. Active Surveillance
4. Comparative Observational Studies
5. Targeted Clinical Investigations
6. Descriptive Studies
E2E Pharmacovigilance Methods

- The best method should be selected
- List not all-inclusive, rather a selection of examples
- There is a strong emphasis on a need to ensure high quality of observational studies used in pharmacovigilance
- The highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed
Stimulated Reporting

- Mostly for new products for early post-authorization (e.g., black triangle schemes)
- EPPV in Japan
- Stimulation after notification of certain risks, not managed by the MAH
- MAH planned stimulation also possible to gather more information on certain safety issues
- Handled as spontaneous reports
Active Surveillance

• Seeks to ascertain completely the number of adverse events via a continuous pre-organized process.

• Examples described include:
  • Sentinel Sites
  • Drug Event Monitoring
  • Registries
Comparative Observational Studies

- Cross-Sectional Study (Survey)
- Case-Control Study
- Cohort Study
- Use of databases
Targeted Clinical Investigations

• PK and PD studies
• Genetic testing
• Interaction studies (drug-drug, drug-food)
• In special populations
• “Large simplified trial”
Descriptive studies

- Natural History of Disease
- Drug Utilisation Study
Which method and when?

• Routine pharmacovigilance (spontaneous reporting) is recommended for all products
• Enhanced/focused pharmacovigilance is better carried out under specified conditions when safety issues or potential safety issues need to be addressed
• Active studies are undertaken when data is needed quickly
  • They often provide denominator values and thus useful for estimating burden/frequencies of events
• Some studies may be demanded by national authorities as part of the conditions for registration
Post-Authorisation Safety Studies PASS

- EU Guideline on good pharmacovigilance practices (GVP)
- Module VIII – Post-authorisation safety studies (Rev 1)
A post-authorisation safety study (PASS) is defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
Conditions for PASS - I

• A PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily, or pursuant to an obligation imposed by a competent authority

• These studies shall be conducted in accordance with the following provisions:
Conditions for PASS - II

• A PASS may be managed or financed by a marketing authorisation holder pursuant to an obligation imposed by a competent authority including:
  • Studies imposed as an obligation in accordance with
  • Studies imposed as a specific obligation in the framework of a marketing authorisation granted under exceptional circumstances

• A PASS initiated, managed or financed by a marketing authorisation holder voluntarily, namely those that have not been imposed as an obligation;
  • they include those required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimisation
PASS or PAS

- Post Authorisation studies are of two types
  - Post Authorisation Efficacy Studies (PAES)
    - Interventional
    - Non-interventional
  - Post Authorisation Safety Studies (PASS)
    - Interventional
    - Non-Interventional
Types of PASS

• Post-authorisation safety studies are of two types
  • Clinical Trials
  • Non-interventional studies
Non-interventional studies

- A PASS is non-interventional if the following requirements are cumulatively fulfilled:
  - The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
  - The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
  - No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.
Non-interventional studies

- Non-interventional studies include:
  - Database research or review of records where all the events of interest have already happened
    - E.g. case-control, cross-sectional, cohort or other study designs making secondary use of data
  - Non-interventional studies also include those involving primary data collection
    - E.g. prospective observational studies and registries in which the data collected derive from routine clinical care, provided that the conditions set out above are met
    - In these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice
Objectives of PASS – I

• To quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;

• To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);
Objectives of PASS - II

• To evaluate the risks of a medicinal product after long-term use;
• To provide evidence about the absence of risks;
• To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
• To measure the effectiveness of a risk minimisation activity
Imposition of PASS

The FDA may impose a PASS on any MAH for several reasons including, but not limited to:

• As part of the initial marketing authorisation application
• During a post-authorisation regulatory procedure
• Due to an emerging safety concern
• Joint post-authorisation safety studies by different MAHs in response to safety issues or when rare events are identified
Methods for Post Authorisation Safety Studies
PASS Methods

• Active Surveillance
• Observational Studies
• Clinical Trials
• Drug Utilisation Studies
Active Surveillance

- Seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process
  - E.g. follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission for later contact
- Active surveillance gives more comprehensive data on individual adverse event reports than passive reporting system
- Automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may also provide an efficient active surveillance system
Active Surveillance - Types

- Intensive monitoring schemes
- Prescription event monitoring
- Registries
Observational studies

- Traditional epidemiological methods are a key component in the evaluation of adverse events.
- There are a number of observational study designs that are useful in validating signals from spontaneous reports, active surveillance programmes or case series.
Types of Observational Studies

- Cross-sectional study (survey)
- Case-control studies
- Cohort Study based on primary data collection or secondary use of existing data
- Other study designs
  - Designs to assess the association between intermittent exposures and short-term events, including the self-controlled case-series, the case-crossover and the case-time-control studies
Clinical Trials

When significant risks are identified from pre-approval clinical trials, further clinical trials might be called for to evaluate the mechanism of action for the adverse reaction.

In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events.

Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions

- Pharmacogenetics; Personalised medicine
Types of Clinical Trials

- Large simple trials
- Other types
Drug utilisation studies (DUS) describe how a medicinal product is prescribed and used in routine clinical practice in large populations, including elderly patients, children, pregnant women or patients with hepatic or renal dysfunction, who are often excluded by randomized clinical trials.

- Stratification by age, gender, concomitant medication and other characteristics allows a comprehensive characterization of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes.
- From DUS, denominator data may be derived for use in determining rates of adverse reactions.
Drug Utilisation Studies - II

• DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions

• DUS may be used to examine the relationship between recommended and actual clinical practice

• DUS may help to monitor use in everyday medical practice and medication error and to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing
PV during use of medicinal products in special situations - Pregnancy

- Reports, where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth.
PV during use of medicinal products in special situations - Pregnancy

- Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported as such.
  - This includes reports of congenital anomalies or developmental delay, in the foetus or the child;
  - reports of foetal death and spontaneous abortion; and
  - reports of suspected adverse reactions in the neonate that are classified as serious.
Special Situations - Breastfeeding

- Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported.
Special situations – Elderly or Paediatric Population

• Collection of safety information in the paediatric or elderly population is important
  • Reasonable attempts should therefore be made to obtain and submit the age or age group of
    the patient when a case is reported by a healthcare professional, or consumer in order to
    be able to identify potential safety signals specific to a particular population

• Paediatric PV is growing in importance with published guidelines
Overdose, abuse, off-label use, misuse, medication error or occupational exposure

• Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or consumer.

• Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in periodic safety update reports as applicable.
Summary

• There are several types of pharmacovigilance methods
• In addition to spontaneous reporting, other methods may be used
• Regulators may impose additional post authorisation studies
  • MAH may voluntary undertake these as well
Comments, Questions etc