



Basic Elements of a PV system

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Basic Elements of a PV system

- Safety information workflow
- Safety databases
- PV personnel & service providers
- PV data sources
- Individual reports
- Aggregate reports



Basic Elements of a PV system – safety information workflow

Safety information

Clinical trials
Post marketing studies
Health Care Professionals
Patients
Literature
Media
...

Global Safety Database

Benefit risk assessment

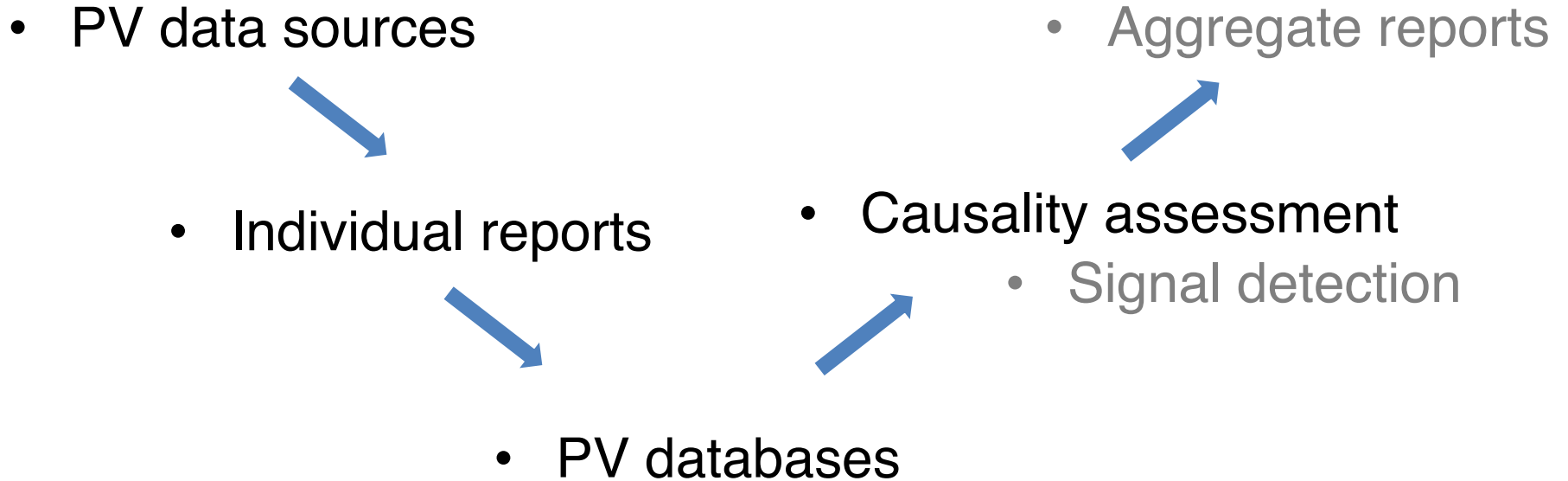
I
N
F
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M

Authorities
HCPs
Patients





Basic Elements of a PV system



COLLECT → **STORE** → **ANALYSE** → **COMMUNICATE**



Basic Elements of a PV system

Safety information workflow

Notion of single collection point

- Sources of safety information are various and MAH must ensure that **all** potential sources within its organisation are identified
 - MAH should ensure that all safety information is received at one single collection point within the organisation
 - The single collection point can be internal or external (PV service provider) but must be communicated to all relevant parties within and outside the organisation
- ➔ Importance to keep contact information up to date in all places where safety information can be exchanged



Basic Elements of a PV system – safety information workflow

Collection & storage of safety information

- Identify all documents that can be part of the PV activities
- Define what are the elements of a case file
- Define what is stored and how it is stored including back up procedure and disaster recovery plans
- Define retention periods of documents by type of document



Basic Elements of a PV system

PV personnel and PV service providers

PV Personnel and PV service providers

- MAH must have qualified and fully trained personnel for the performance of PV related activities
- Qualification and training aspects in scope of inspections
- Ongoing training and ongoing monitoring of training compliance is key
- Training also of company non PV personnel
- Assessment of training effectiveness



Basic Elements of a PV system

PV personnel and PV service providers

- MAH can outsource all or some of the PV related activities
- PV service providers must be audited before outsourcing of activities
- Key to identify the best service provider for the activities to be outsourced



Basic Elements of a PV system

Safety databases

Safety databases

- Commercially available safety databases
- Company validated safety databases
- Eudravigilance
- Excel and other non-validated systems
- Paper based repository



Basic Elements of a PV system

Safety databases

Considerations

- No legal obligation for MAH to use a commercially available safety database
- Selection of database/system will mainly be based on business model and case volume
- Case volume is sometimes difficult to anticipate and may result in selection of an inadequate PV system



Basic Elements of a PV system

Safety databases

Commercially available safety databases

- Fully E2B compliant
- Allow a lot of automation, integrated rules & customisation
- Allow electronic reporting to EEA and FDA
- Easy tracking of changes (audit trails)
- Easy generation of standard ICSR reports (CIOMS I, MedWatch, etc) and listings/tabulations



Basic Elements of a PV system

Safety databases

- Allow generation of blinded and unblinded reports
- Integrated communication modules
- Xml transfers from 1 DB to another
- Integration of customisable charts & tables for case volume & compliance metrics
- Access by multiple users with different rights & roles
- Modules for local contact persons with automated transfer into the global safety database



Basic Elements of a PV system

Safety databases

BUT

- Costly
- Remote helpdesk and 'generalists' who can not always help with very specific issues
- Customisation require usually a lot of 'UATs' (user acceptance tests)



Basic Elements of a PV system

Safety databases

Company validated safety databases

- Flexibility
- 1 system for 1 company
- Can be customised to the finest details (can go beyond E2B requirements)
- Usually quicker implementation of changes



Basic Elements of a PV system

Safety databases

BUT

- Costly
- Require up to date regulatory intelligence & E2B requirements



Basic Elements of a PV system

Safety databases

Eudravigilance (EMA)

- For MAH registered with Eudravigilance, ICSRs can be generated within the system and submitted when required to the relevant competent EEA authorities
- Need to be certified user to get access and create ICRS
- MAH can delegate access to a PV service provider
- No costs
- Use of integrated dictionaries (MedDRA and xEVMPD)
MAH must nevertheless have its own MedDRA license



Basic Elements of a PV system

Safety databases

- E2B compliant
- Possibility to produce xmls, rtf and pdf CIOMS

BUT

- Not a database where MAH's ICSRs can be stored (xmls and other produced outputs must be saved outside of the system). Only expedited reports can be retrieved from the system
- MAH must make sure that it's product information (xEVM DP) is kept up to date



Basic Elements of a PV system

Safety databases

Excel or other internal non-validated tools

- Suitable for low volume of cases
- No extra costs
- Can be customised to integrate relevant information for periodic reports listings and tabulations



Basic Elements of a PV system

Safety databases

BUT

- No validation → RISK of errors
- Need controlled access
- Ususally used in combination with Eudravigilance



Basic Elements of a PV system

Safety databases

Paper based repository

- As per regulations, no obligation to have an electronic repository/DB
- Easy to implement, no validation required

BUT

- No remote access
- Needs storage security (fire proof and access controlled cabinets)
- Think of back up electronic filing



Basic Elements of a PV system

PV data sources

PV data sources

MAHs have the obligation to ensure that all PV related information from any source is collected and processed for all their products.

The sources for safety information are multiple and the MAH must have an exact overview of all potential sources of safety information.

The sources may be divided in 2 main areas

- pre-marketing data collection
- post-marketing data collection



Basic Elements of a PV system

PV data sources

The sources may be divided in 2 main areas

1. Pre-marketing data collection
2. Post-marketing data collection



Basic Elements of a PV system

PV data sources

1. Pre-Marketing data collection

- Phase I to III clinical trials
- SAEs and ESIs (Events of Special Interest) & pregnancies
 - Collection systems and rules are protocol defined
 - Use of clinical and safety databases
 - Provide limited PV information



Basic Elements of a PV system

PV data sources

2. Post-Marketing data collection

- Main source of PV information
- 2 main collection sources
 - Unsolicited sources
 - Solicited sources



Basic Elements of a PV system

PV data sources

- **Unsolicited sources (no organised collection)**
 - Reports from HCPs, patients or consumers
 - Reports from health authorities
 - Reports detected in the medical and scientific literature
 - Lay press, social media
 - Reports identified on the MAHs sponsored web sites



Basic Elements of a PV system

PV data sources

- Reports in the frame of quality complaints or product defects or medical inquiries
- Reports detected in the medical and scientific literature
- Reports identified on the MAHs sponsored web sites
- Reports received via 3rd parties having a contractual arrangement with MAH (service providers, distributors, call centers, licensing partners, etc)



Basic Elements of a PV system

PV data sources

- **Solicited sources (organised collection)**
 - Post marketing interventional clinical trials
 - Post marketing safety studies (PASS)
 - Drug utilisation studies (DUS)
 - Registries
 - Surveys (patients or HCPs)
 - Post approval named patient use programmes or compassionate use
 - ...



Basic Elements of a PV system

Individual reports

What should be collected?

A. Case information

- Reporter information
- Patient information
- Suspect drug information
- Adverse event/Safety related event information

B. Administrative information

- First contact date
- FUP dates
- Expedited reporting dates if applicable
- Internal case processing dates



Basic Elements of a PV system

Individual reports

A. Case information

- Reporter information*
 - Primary source = person who initially reports the facts
 - Secondary source = subsequent reporters (e.g same report received from health authorities, from licensing partner, described in literature, etc)
 - Need contact details for follow-up
 - Consumer reports → seek medical confirmation

***Collect, store and transmit PII (Personally Identifiable Information) according to local data privacy laws**



Basic Elements of a PV system

Individual reports

- Patient information
 - Identifiable patient → at least one of the following elements is required:
 - Age, age group or date of birth*
 - Gender
 - Initials*
 - Medical records number
 - Relevant medical history
 - Relevant concomitant drugs

*** Collect, store and transmit PII (Personally Identifiable Information) according to local data privacy laws**



Basic Elements of a PV system

Individual reports

- Suspect drug information
 - Suspect drug proprietry name/invented name or generic name
 - Administration start and stop dates
 - Dosage (interval and cumulative)
 - Route of administration
 - Dosage form
 - Indication for use
 - **Lot number !**



Basic Elements of a PV system

Individual reports

- Adverse Event information*
 - Event as reported = verbatim
 - Onset date or interval delay between last drug administration and onset of event
 - Course of reaction
 - Seriousness
 - Causality
 - Outcome



Basic Elements of a PV system

Individual reports

- B. Administrative information

- First contact date

Key for expedited reporting (day zero/clock start date)

Date of 1st awareness of a valid case by the MAH or any party having a contractual arrangement with the MAH

Must always be clearly documented on ICSR source documents and in safety DB



Basic Elements of a PV system

Individual reports

- FUP receipt dates

Also relevant for expedited reporting

Every new piece of information needs a receipt date which must be clearly documented on ICSR

- Expedited reporting dates if applicable

Need to be recorded and tracked for compliance metrics for each transmission (competent authorities but also IRBs and EC for clinical trials)



Basic Elements of a PV system

Individual reports

- Internal case processing timelines & metrics

Relevant for compliance wrt safety data exchange agreements and case processing effectiveness.

Helps for benchmarking in case of outsourcing or internal effectiveness measures



Basic Elements of a PV system

Individual reports

Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.



Basic Elements of a PV system

Individual reports

Adverse Reaction

An adverse reaction implies that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.

Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.



Basic Elements of a PV system

Individual reports

BUT not only Adverse Events/reactions need to be collected – scope is broader and should encompass the following:

- Drug interaction (drug-drug or drug-food),
- Exposure during pregnancy (with or without outcome) or lactation
- Lack of efficacy
- Overdose (intentional or accidental)
- Off-label use
- Suspected transmission of infectious disease via the medicinal product
- Drug abuse and misuse
- Accidental exposure
- Medication errors (established or potential) /dispensing errors/maladministrations
- Unintended beneficial effect
- Occupational exposure
- Non-compliance with the prescribed treatment

➔ Safety related events



Basic Elements of a PV system

Individual reports

Serious adverse event:

1. Reporters's seriousness assessment (According to ICH & FDA seriousness criteria)

- Results in death
- Is life-threatening (patient at risk of death)
- Requires in-patient hospitalisation or prolongation of hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Important medical event not meeting any of the above criteria but that might jeopardise the patient or might require intervention to prevent one of the above outcomes

Any suspected transmission of an infectious agent via a medicinal product should also be considered as a serious adverse reaction



Basic Elements of a PV system

Individual reports

2. Company seriousness assessment

In the absence of a reporter's seriousness assessment, the MAH should evaluate the information and can apply internal seriousness to individual events.

Internal seriousness assessment can be based on MSSO IME (Important Medical Events) list or an adapted version thereof and other internal criteria (product related specificities).

An ICH seriousness criterion always prevails an internal assessment which means that if an ICH criterion is met, there is no need to apply also internal seriousness assessment

Internal seriousness is not applied to interventional clinical trials



Basic Elements of a PV system

Individual reports

An important component of pharmacovigilance is the causality assessment i.e the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event.

It assesses the relationship between a drug treatment and the occurrence of an adverse event , contributing to better evaluation of the risk-benefit profiles of medicines.

It is essential though difficult to establish causal relationship between the drug and the event



Basic Elements of a PV system

Individual reports

When is it done, when is it needed?

- Required for cases collected in organised data collection
- Not required for purely spontaneous reports (deemed to be by essence potentially related if reported)
- Essential component of the signal evaluation



Basic Elements of a PV system

Individual reports

Many methods proposed but assessing the causal role of a drug in the occurrence of an adverse medical event remains one of the most controversial issues.

All these methods are classified in three broad categories:

- expert judgement/global introspection
 - Swedish Method by Wilholm
 - WHO - UMC causality assessment criteria
- algorithms
 - French imputability
 - Kramer et al.
 - Naranjo et al.
- probabilistic methods (Bayesian approaches)

But no single method is universally accepted



Basic Elements of a PV system

Individual reports

Causality assessment in vaccine case reports

Although vaccines rarely cause serious adverse events, some conditions coincidentally associated with vaccines have caused and still may cause public concern resulting in a decrease of vaccination coverage and in subsequent epidemics.

Most of the solid evidence regarding the association of an specific AE and a vaccine comes from carefully designed epidemiological studies assessing absolute or relative risks.



Basic Elements of a PV system

Individual reports

- Need systematic assessment of single episodes or of clusters of serious and unexpected AEFIs (Adverse Events Following Immunisation) to achieve highest safety in immunisation programs and maintain public confidence



Basic Elements of a PV system

Individual reports

→ Points to consider when evaluating the causality

biological plausibility, time elapsed between the vaccine administration and the onset of the adverse event, de-challenge & re-challenge information, drug-class effect, other potential contributing factors (drugs, chemicals or underlying disease),



Individual reports – Causality assessment specific to Vaccines

Global Advisory Committee for Vaccine Safety (GACVS)

- Established in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance
- Provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programmes
- Review the WHO Adverse Event Following Immunisation (AEFI) causality assessment
- Develop a standardised method to help assessing the causality of vaccine related events



Individual reports – Causality assessment specific to Vaccines

The ACCA (Advisory Committee on Causality Assessment)

The ACCA in Canada has developed a method for causality assessment.

The most serious and unusual reactions requiring detailed review are submitted to ACCA.

The ACCA is composed of specialists in paediatrics, epidemiology, infectious diseases, immunology, neurology, pathology, adverse event surveillance, and microbiology and has been reviewing individual cases in a systematic stepwise manner to categorize them on a specially designed causality assessment form going through several points.



Basic Elements of a PV system

Aggregate reports

Aggregate reports

- Pre-registration
- Post-registration



Basic Elements of a PV system

Aggregate reports

Pre-registration aggregate reports

- Mandatory for all products under development
- Schedule and content may vary according to receiving authority
- Waivers can be obtained regarding the format for FDA reporting (DSUR format)
- Sponsor responsibility for these reports but may be outsourced



Basic Elements of a PV system

Aggregate reports

Post-registration aggregate reports

- Mandatory for almost all products with a MAH
- In EU – EURD schedule and also dependant on the MA
- Responsibility of the MAH but can be outsourced