Training in Pharmacovigilance

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Collecting Good Quality Safety Information

- What information to collect?
- Why the need for good Quality Safety Information?
- What constitutes good safety information?
- Differing regulations concerning safety data collection requirements
- Designing a system to collect good quality information
The key reason for provision of Adverse reaction data is:

- Patient Protection
- Regulatory Compliance
- Company Protection

In order to judge the safety of the Company product it is essential that not only is the reaction reported but that the Company can assess (wherever possible) if the reaction can be explained (or dismissed) as having a causal relationship to the product.
Collecting Good Quality Safety Information

The key reason for provision of Adverse reaction data is:

Additionally, the information provided may enable the Company to determine whether the adverse reaction could be preventable for all of the patient population or for a specific section of the treated population:

Risk Management/Minimisation REMs

It must also be remembered that not all drug administrations to patients are in accordance with the prescribing information present in the SmPC and so it is essential to confirm correct usage of the Company product (Off label; misuse; abuse; error etc...)
What information to collect?
Collecting Good Quality Safety Information

Types of Information:

- Serious ADR
- Non-serious ADR
- SAE
- Non-serious AE
- Consumer
- HCP

Signals
- Open
- Closed

Labelling
- CCSI
- SmPC

RMP
- Minimise
- Manage
Collecting Good Quality Safety Information

Types of Information:

- Overdose
- Abuse; Misuse
- Pregnancy & lactation
- Off label
- Occupational exposure
- Medication Error

Database

Signals
- Open
- Closed

Labelling
- CCSI
- SmPC

RMP
- Minimise
- Manage
Types of Information:

Lack of efficacy
Patient population risk
Elderly & Paediatric
Product specific ADRs

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Signals
Open | Closed

Labelling
CCSI | SmPC

RMP
Minimise | Manage

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Collecting Good Quality Safety Information

The case report:

Minimum information = valid report
Safety Data Triage and assessment

- Case assessment for Seriousness and Expectedness – expedited case determination

- Case assessment for completeness of data – quality review elements:
  - Patient demography (age, gender, ethnic origin)
  - Suspect product (dosage; route; cumulative dosage)
  - Healthcare professional confirmation
  - Adverse reaction(s) (Diagnosis, sign, symptom) Causality assessment on each ADR
  - Relevant medical history (including any other risk factors weight, smoking, alcohol)
  - Suspect product duration of exposure
  - Adverse reaction onset date
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Case assessment for completeness of data – quality review elements:

- ADR outcome and resolution date
- ADR sequelae
- Indication (approved versus unapproved)
- Concomitant medication (including therapy dates, dosages)
- Seriousness determination
- Dechallenge information
- Rechallenge information
- Diagnostic data (where applicable)
- Cases involving death (death certificate, autopsy report)

Data quality is essential for case assessment and signal strength determination
Why the need for good Quality Safety Information?
Collecting Good Quality Safety Information

If information is missing for any case then it is difficult to assess a case to ensure:

• Patients are adequately protected by the Company in ensuring ADR information is accurately reflected in any Regulatory information (SmPCs, PILs)

• To provide accurate Information to Prescribers to treat patients effectively

• To minimise risk to individual patients or patient populations by quickly assessing risks and communicating information to prescribers and patients

• To demonstrate fast, reactive response to Regulatory Authorities in taking action to protect patients

• To ensure that the safety of the Companies products (either as an investigational or marketed products) is maintained
If information is missing for any reported case then it is more difficult to assess a case to ensure:

- Makes it difficult to assess Company causality (Regulatory requirement)
- To understand the mechanism by which adverse reactions can appear
- The time course to its appearance/disappearance
- How it may be treated or prevented
- Whether any sequelae
- To understand how certain reactions can be minimised or managed
Collecting Good Quality Safety Information

Designing a system to collect good quality information
Collecting Good Quality Safety Information

Collection of information should be:

- Simple
- Concise
- Pertinent

If information has not been provided at the first opportunity then a system of obtaining follow-up information needs to be in place.

Requests for follow-up information needs to be according to the importance of the reported event:

- Serious Unexpected Adverse Drug Reaction (SUADR)
- Serious expected Adverse Drug Reaction (SADR)
- Non-Serious Unexpected Adverse Drug Reaction (NSUADR)
- Non-serious expected Adverse Drug Reaction (NSADR)
- Serious Adverse Event (SAE)
- Adverse Event (AE)
Frequency of trying to obtain follow up information:

- **SUADR** – 3 attempts, 2 weeks apart?
- **SADR** – 3 attempts, 2 weeks apart?
- **NSUADR** – 3 attempts, 2 weeks apart?
- **NSADR** – 2 attempts, 2 weeks apart?

There is no strict Regulatory definition requiring certain timelines for follow up.

**ICH E2D** – Triage for Safety, focus on those cases which require your major efforts –

which would be:
The triage sequence:

Most Important:
- Serious unexpected + Fatal
- Serious unexpected – permanent damage

Intermediate:
- Serious unexpected (sequelae?)
- Serious expected (mechanism unknown)

Least Important:
- Non-Serious unexpected
- Non-Serious expected
Unexpected Adverse Drug Reactions: (ICH E2D; E2A; E2C)

An ADR whose nature, severity or specificity or outcome is not consistent with the term or description used in the official product information should be considered unexpected.

An ADR with a fatal outcome should be considered unexpected, unless the official product information specifies a fatal outcome for the ADR. If the fatal outcome is recorded then the ADR should be handled as an expected ADR.

*In the absence of sufficient documentation regarding the ADR then with the uncertainty the reaction should be considered as unexpected*
Other considerations for expected/unexpected ADRs:

Class ADRs should not be automatically considered as expected. Class ADRs should not be considered as expected unless the ADR has been specifically seen with the product.

If the ADR has not been seen specifically with the product but a Class labelled ADR is present then the ADR should be considered as unexpected.
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Sources of Individual Safety Case Reports (ICSRs)
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Sources of Cases:

- Clinical Trials
- Spontaneous Cases
- Observational Studies
- Literature
- Internet – Social Media
Sources of Individual Case Reports:

Unsolicited Reports = Spontaneous reports

A unsolicited communication by an HCP or consumer to a Company, regulatory authority, or other organization (e.g. poison control centre) that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any other organised collection scheme.

Stimulated reporting may arise when sending out a Dear Dr letter but these will still be regarded as spontaneous cases.
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Sources of Individual Case Reports:

Unsolicited Reports

- Consumer reports

  Should be regarded as spontaneous cases irrespective of medical confirmation.

  All cases should be retained even if there is no medical confirmation.

  Emphasis is on the quality of the report not the source.

- Literature

  The MAH is expected to screen world-wide scientific literature for such reports. The reporting clock begins once the Company has identified the 4 minimum item reporting criteria.

  Recommends searches according to local regulations or at least once a month.
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Sources of Individual Caser Reports:

Unsolicited Reports:

Internet

- MAHs are not expected to screen external websites for ADRs?

- MAHs with websites should screen these regularly for ADRs and provide mechanisms of reporting e.g. ADR forms.

Either of these sources are regarded as spontaneous

- Other sources

Any reports from non-medical sources should be regarded as spontaneous
Sources of Individual Case Reports:

Solicited Reports

These arise from organised data collection systems e.g. clinical trials; post-approval named patient use programs; patient support and disease management programmes; surveys of patients or healthcare providers or programmes of efficacy and patient compliance

These should not be considered as spontaneous.

Solicited reports should be handled as if they were study reports and should have appropriate causality assessments. For blinded therapies, further guidance should be derived from ICH E2A
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Sources of Individual Case Reports:

Licensor – licensee Interactions:

    Co-development; co-marketing; co-promotion – recommendation for explicit safety agreement which details processes for reporting including timelines and reporting responsibilities (who does what where when and how). The MAH is ultimately responsible

Total time for expedited reporting has to be 15 calendar days (from partner to MAH to Regulatory Authority) for any ADR meeting minimum 4 basic reporting criteria.

The MAH who provided the initial report is also responsible for the follow up and submission.
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Sources of Individual Case Reports:

Regulatory Authority Sources:

Individual serious unexpected ADR reports originating from foreign regulatory authorities are always subject to expedited reporting. Re-submission of serious ADR cases without new information to the originating Regulatory Authority is not required.

Onward reporting to other agencies will be required according to local regulations.
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Good Case Management Practices
Training of personnel for pharmacovigilance

- Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel.

- All personnel involved in the performance of pharmacovigilance activities shall be provided with appropriate instructions on critical processes, including business continuity.
Training of personnel for pharmacovigilance

- They shall receive initial and continued training in order to maintain and develop their competencies in accordance with training plans. For marketing authorisation holders, initial and continued training relates specifically also to the roles and responsibilities of personnel.

- The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities.
Training of personnel for pharmacovigilance

- All staff members should receive and be able to seek information about what to do if they become aware of a safety concern.
- There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, and in line with agreed professional development plans.
Training of personnel for pharmacovigilance

• Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, sales and marketing, regulatory affairs, legal affairs and audits.
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The role of Narratives:

Objective: to summarise all relevant clinical and related information including patient characteristics, therapy details, medical history, clinical course of the events, diagnosis and ADR(s) [to include outcome (of each ADR); laboratory evidence to support or refute the ADR. Narrative should be a comprehensive stand alone medical story.

The narrative should be presented chronologically in terms of the patients experience rather than the order in which the information was obtained.

Abbreviations and acronyms should be avoided where possible.

Autopsy and post-mortem findings should be included

All aspects of the narrative should be appropriately and accurately coded
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Single case evaluation:

Purpose of Medical review is to ensure correct interpretation of medical case content. This will include:

Is a diagnosis possible (versus signs and symptoms)?

Were relevant diagnostic procedures performed (e.g. laboratory analyses)?

Have other possible causes of the ADR been assessed?

The Company should not infer or extrapolate information to provide a diagnosis but stay accurate to the reporters verbatim report. However, diagnostic/laboratory information should be challenged upon follow up to determine if the information supports the conclusion of the reporter.

For consumer reports, any ADR information should be presented to their treating healthcare professional in order to provide a more accurate medical determination, if possible.
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Follow up Information:

Recommendation to prioritise case reports by importance:

Serious and unexpected

Serious and expected

Non-Serious and unexpected

Cases of special interest (ADRs under surveillance; non-serious ADRs which may develop into serious ADRs (mild blood alterations indicating dyscrasias; liver enzyme fluctuations etc.))

Follow up can be obtained by:

Telephone; site visit; written request

Written confirmation should be obtained wherever possible for the data supplied
Follow up Information:

Judgement should be exercised for the extent of follow up and should be placed alongside the seriousness of the reported reaction and the known outcome (condition stabilised; resolved)

It is recommended that MAHs should collaborate together if there is more than one MAHs drug suspected as a causal agent (interactions)

ICH E2D has a list of key data elements which should be included wherever possible in expedited reports
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Follow up related to pregnancy:

Any pregnancy outcome where the reporter or Company decides may be related to the Company product, this should be reported as an expedited report under 15 calendar day rules.

All pregnancy cases should be followed to term.

If the Company product has long half life (or metabolites) even though the product was stopped before conception there is a possibility that drug/metabolite exposure could occur and recommendations in the label and for Company monitoring should occur.
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How to Report:

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MedDRA coded – Properly coded

Electronic transmission

Further support for better reporting:

Electronic ADR forms

Training! Training! Training!
Any Questions

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