Module 11 : Handling special Scenarios

(Pregnancy/lactation, Medication errors/ Overdose/Abuse/Misuse/ Interactions/ Lack of efficacy/STIAMP

Pregnancy or breast feeding

- Drug exposure during pregnancy means the embryo or foetus may have been exposed to medicinal products:
  - Either through maternal exposure and/or
  - If the suspected medicinal product was taken by the father
- Examples:
  - Patient was pregnant and then started taking a drug
  - Patient was taking a drug and then became pregnant. She stopped taking drug straight away, but it is still a pregnancy case
  - Patient took drug during pregnancy. Pregnancy and Baby completely fine
  - Patient had been taking a drug. Became pregnant six months after stopping it
  - Patient was taking a product and his wife became pregnant – this is also a Pregnancy case

Pregnancy or breast feeding: Contd.

- **Drug exposure via breast feeding** means a product is taken by a mother who is breast feeding, the neonate can get exposed to the drug via breast milk

- The majority of medicinal products or chemical substances administered to a pregnant woman could have effects on the foetus either before the placenta is fully developed or subsequently, if they can cross the placenta to at least some extent.

Pregnancy or breast feeding: Contd

- Medicinal products may have a different impact at different stages of pregnancy.
- The spectrum of effects varies according to the period of exposure. For example:
  - Exposure to a teratogenic agent during the period of organogenesis may induce major malformation, growth retardation or death,
  - While exposure during the second or third trimester may induce growth retardation, renal insufficiency, neurological disorders, stillbirth, etc.
  - On the other hand, exposure to a teratogenic agent during the first two weeks of pregnancy (3rd and 4th gestational week) may lead
    - Either to the death or to a normal pre embryo according to the "all or nothing rule"; at this period zygotes and blastocysts contain omnipotent stem cells without any differentiation, therefore, teratogenic agents may lead to seriously damaged pre embryos, which will not survive,
    - or to less seriously damaged pre embryos, which will survive with complete regeneration.

Pregnancy or breast feeding: Contd

- Drug treatment of male patients prior to or around the time of conception and/or during pregnancy could affect the offspring due to a drug-induced defect in the spermatozoon itself such as an effect on the DNA or chromosome or due to an effect caused by the presence of the drug in the seminal fluid.
- Spontaneous reports of pregnancy exposure are the most common source of post-authorisation data available on the safety of medicinal products in pregnancy.
- Sources include databases of regulatory authorities, national congenital anomaly registries, MAHs and the National Association of Medical Examiner's Pediatric Toxicology (PedTox registry (US).

General recommendations for pregnancy/ lactation

- The minimum required data elements for the reports of adverse outcomes (e.g. congenital abnormality etc.) and data on pregnancy exposure with or without ADR are similar to those required for any ADR report, i.e.
  - An identifiable patient,
  - An identifiable reporter,
  - A suspected ADR and
  - A suspected medicinal product.

General recommendations for pregnancy/ lactation.

- All the specific data elements necessary for the assessment of cases of pregnancy exposure should be included in the narrative, such as:
  - The type of report: retrospective or prospective
  - Information on exposure to medicinal products during pregnancy should include dates of exposure as accurately as possible.
  - Exposure to other teratogens
  - The results of examinations performed: foetal ultrasound, amniocentesis, laboratory tests, etc.

Creation of parent-child/foetus cases

If the child/foetus experiences suspected adverse reactions other than early spontaneous abortion/foetal demise:

- Information on both the parent and the child/foetus should be provided in the same report.
- This case is referred to as a parent-child/foetus report

Both the parent and child/foetus experience suspected adverse reactions other than early spontaneous abortion/foetal demise:

- Two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created.

Creation of parent-child/foetus cases

No reaction is affecting the child/foetus:

- Only a parent report should be created to describe the child exposure to the medicinal product.
- The patient characteristics refer only to the parent (mother or father) who may as well experience adverse reactions with the suspected medicinal product.
- Reports with no reaction should not be submitted as ICSRs

Miscarriage or early spontaneous abortion is reported:

- Only a parent report is applicable with the patient's characteristics to be provided for the mother. However, if the suspect medicinal product was taken by the father, this information should also be recorded.

ICSR for pregnancy exposure

1st situation: ADR reported in mother	
Spontaneous abortion	1 case « mother »
Foetal death without information on malformation	1 case « mother »
Foetus with defects	2 cases: 1 case « mother » and 1 case « foetus » but cases linked
Birth defects or ADR in baby	2 cases: 1 case « mother » and 1 case « foetus » but cases linked
No ADR in child	1 case « mother »
2nd situation: No ADR in mother	
Spontaneous abortion	1 case « mother »
Foetal death without information on malformation	1 case « mother »
Foetus with defects	1 case « foetus »
Birth defects or ADR in baby	1 case « baby »
No ADR in child	No case
Particular situation: Twins	
One case for each twin	

Submission of ICSRs

- Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as **serious reports**. This especially refers to:
  - 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

Submission of ICSRs

Following repots should not be submitted as ICSRs since there is no suspected adverse reaction

- Reports of induced termination of pregnancy without information on congenital malformation
- Reports of pregnancy exposure without outcome data
- Reports which have a normal outcome.

These reports should however be collected and discussed in the periodic safety update reports

Important points

- When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo through the mother and/or the father if the medicinal product was taken before conception.
- Reports concerning drug exposure during pregnancy and/or breast feeding should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth

Overdose, abuse, misuse, medication error or occupational exposure

- **Overdose (OD)**: Administration of a quantity of a medicinal product given per administration or cumulatively, which **is above the maximum recommended dose** according to the authorised product information.
- **Misuse**: Medicinal product **is intentionally and inappropriately u**sed not in accordance with the terms of the marketing authorisation.
- **Abuse**: This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Occupational exposure (OE):** Exposure to a medicinal product, as a result of one's professional or non-professional occupation.
- **Medication error (ME)**: An unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient

Overdose, abuse, misuse, medication error or occupational exposure

Reports of OD/abuse/misuse/ME/OE

- With no associated suspected adverse reaction should not be submitted as ICSRs.
- Reports associated with suspected adverse reactions should be subject to submission
- Along with the resulting suspected adverse reactions, an appropriate MedDRA LLT term corresponding most closely to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be specified in the ICH-E2B section ‘Reactions/Events’.

Special situation: Overdose

- If an adverse event (AE) develops following an overdose, the event will be considered as expected/listed if it is clearly mentioned in the RSI.
- The events, which are mentioned/stated in the overdose section, should be used only to assess expectedness/ listedness for overdose cases.
- *Therefore if a drug was not taken as an overdose, the resulting events should not be assessed against the overdose section.*
- Non-fatal overdose (non-serious and serious) is always listed.

Note: Fatal overdose should be specifically mentioned in the overdose section for listedness.

Special situation: Medication error

- A medication error should be considered as expected.
- Suspected (serious and non-serious) Aes associated with medication errors, i.e. where the suspected AE is a direct response to the medicinal product and was caused by an error, should be recorded, reported and assessed
- If a case of ME is reported with clinical consequences, the MedDRA Lowest Level Term (LLT), corresponding to the term closest to the description of the reported medication error should be added to the term for the suspected adverse reaction in the data element 'Reaction/event in MedDRA terminology (LLT)' in line with the recommendation of MTS: PTC

Special situation: Medication error

- Medication errors may trigger a series of events and there may be more than one stage in the drug treatment process affected by an error, e.g. a prescription error, if not intercepted, would lead to a dispensing error and consequently result in an administration error.
- For coding purposes it is most important to capture the primary stage of the medication process where the error first occurred (e.g. prescribing error) and any subsequent error reaching the patient (e.g. administration error), including the clinical consequences for the patient

Special situation: Medication error

- A medicinal product may be prescribed and administered to a patient in whom it is contraindicated, because the prescriber or caregiver is unaware that there is a contraindication labelled in the RSI. This should be coded with the LLT Contraindicated drug administered
- Where a medicinal product is prescribed and administered to a patient in whom it is contraindicated, because the prescriber or caregiver is unaware that the patient has a disease that causes the drug to be contraindicated, the LLT Labelled drug disease interaction medication error should be coded
- If the prescriber knows that a medicinal product is contraindicated, but intentionally prescribes it anyway this is considered off-label use and should be coded accordingly.

Special situation: Medication error

- Patient non-compliance with a prescribed treatment or course of medication may result from a variety of factors and a common scenario is intentional non-compliance if the patient decides not to take the prescribed medicine (e.g. antibiotic course not completed) because the patient feels better.
- If there is an element of intention implied, this would not be considered a medication error.
- Circumstances of treatment non-compliance which cannot be coded with appropriate MedDRA terms should be provided in the narrative.
- Intentional re-challenge to a medicinal product should not be considered a medication error and not be coded as such.

Special situation: Medication error

- If it is not possible to establish whether the event occurred due to an intentional decision made by the healthcare professional, patient or consumer, or whether it occurred unintentionally, it may be appropriate to use a more general MedDRA term from the HLT - Product use issues NEC.
- Lack of efficacy of a medicinal product is not considered a medication error per se.
- There may be medication errors which lead to a lack of efficacy in the patient, for example where a patient has accidently received an underdose.
- The coding should reflect the error and include e.g. the PT Drug ineffective.

Special situation: Medication error

- If a patient is unable to get a (repeat-) prescription (e.g. from pharmacy or from emergency supplies) or due to a manufacturing defect and as a consequence the patient experiences a deterioration of the underlying condition, this is not considered a medication error.
- A product availability issue could be coded with LLT Drug supply chain interruption
- Accidental exposure is not defined in GVP and may refer to acute, sudden exposure in context of an accident which could also be the result of a ME depending on the circumstances.
- Occupational exposure is generally not considered a ME, however for pharmacovigilance purposes if the exposure happened suddenly and accidentally it may well be considered an error which should be coded with appropriate MedDRA terms to reflect both the ME and the occupational exposure

Off-label use versus medication error and misuse

- Medication errors should be clearly distinguished from off-label use.
- Off-label use relates to situations where the medicinal product is ***intentionally*** used for a medical purpose not in accordance with the authorised product information
- Medication error however refers to any **unintended failure** in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.
- Medication errors should be clearly distinguished from misuse.
- Misuse relates to situations where the medicinal product is **intentionally and inappropriately** used not in accordance with the authorised product information.
- For cases where a patient has misunderstood the instructions for how to use the medicine correctly, this should be considered an error and appropriate MedDRA terms selected to represent the event, e.g. LLT Tablet crushed incorrectly.

Overdose/underdose versus medication error

- Overdoses are not necessarily considered to be ME unless *unintentional* overdose occurred as a consequence of an error.
- In this situation it is important to code both concepts in order to facilitate case identification.
- Intentional overdose is not considered a ME.
- For the purposes of term selection and analysis of MedDRA-coded data,
  - Overdose means more than the maximum recommended dose (in quantity and/or concentration), i.e. an excessive dose,
  - Whereas underdose is the administration of less than the minimum recommended dose (in quantity and/or concentration).
- Both over- and underdose may unintentionally be the result of a preceding medication error and relevant terms from the HLT Maladministrations may be chosen in combination with the associated medication error term.

Product quality issue versus medication error

- Product quality issues are abnormalities that may be introduced during the manufacturing, labelling, packaging, shipping, handling or storing process of a medicinal product.
- They should be distinguished and carefully evaluated if they fall in the definition of a medication error.
- For example, an underdose of antibiotic was administered because the lines on the dropper were hard to read which led to a medication error (accidental underdose).
- Medication errors involving a drug delivery device may be related to wrong use of the device with clinical consequence for the patient related to the drug.
- The *HLT Maladministrations* contains terms for errors associated with drug delivery devices. Other terms in the *HLGT Device issues* may be relevant as appropriate.

Medication error related to names

- For reporting an (invented) name confusion as ICSR, the names of both medicinal products involved in the confusion should be provided in the drug section regardless of whether the sender holds a marketing authorisation for both products.
- In ICH E2B (R3) format the product which the patient received by mistake should be given the drug characterisation 'suspect' and the product which was not received (because of the error) should be assigned the characterisation 'drug not administered'.
- The MedDRA terms selected should indicate the name confusion and any other associated medication errors and adverse reactions.

Special situation: Lack of efficacy (LOE)

- Lack of efficacy should be considered as expected because no drug is expected to be 100% effective in all patients
- Reports of LOE should be collected and recorded when notified and followed-up if incomplete.
- They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in PSURs as applicable.
- In certain circumstances, reports of LOE with no suspected adverse reactions may require to be submitted within a 15-day time frame:
    - If single cases give rise to the suspicion of product related issues (e.g. counterfeit).
    - Medicinal products used for the treatment of life-threatening diseases
    - Vaccines
    - Contraceptives

Lack of efficacy (LOE)

- The ICSRs should be submitted within a 15-day time frame even if no seriousness criterion is specified.
- Progression of an underlying disease, when reported and qualified for entry as an AE, should be considered unexpected/unlisted unless it is specifically described in the reference safety information.
- Unless aggravation of the medical condition occurs, the indication for which the suspected medicinal product was administered should not be included in the ICH-E2B section ‘Reactions/Events’.
- If the primary source suspects a LOE, the MedDRA LLT term, corresponding most closely to the description of the reported lack of therapeutic efficacy, should be specified in the ICSR

Specific situation: Interaction

- For the event of drug interaction to be considered as expected/listed, the drug interaction should be described in the appropriate section of the labelling document together with the second suspect drug or drug class.
- The symptoms attributed to the interaction are expected if they are clearly noted as expected/listed in the drug interaction section or other appropriate sections.
- Events mentioned in the interaction section should only be considered expected/listed if the patient received both specified drugs.

Specific situation: STIAMP

Suspected Transmission of Infectious Agents via a Medicinal Product

- All reports of Suspected Transmission of Infectious Agents via a Medicinal Product (STIAMP) should be processed as medically significant, unless another serious criterion is applicable, and unexpected/unlisted in all labelling documents.
- if the infectious agent is specified in the report, the MedDRA LLT term corresponding most closely to the infectious agent should also be included in the ICSR

Thank you

Assessment

Question: 1

All reports of Suspected Transmission of Infectious Agents via a Medicinal Product (STIAMP) should be processed as medically significant, unless another serious criterion is applicable, and unexpected/unlisted in all labelling documents.

Above statement is :

a). True

b). False

Question: 2

Reports of lack of therapeutic efficacy with no suspected adverse reactions for vaccines may require to be submitted within a 15-day time frame.

Above statement is :

a). True

b). False

Question: 3

_____ means more than the maximum recommended dose (in quantity and/or concentration), i.e. an excessive dose

a). Overdose

b). Underdose

c) Both

d) Medication error

Question: 4

Intentional re-challenge to a medicinal product should be considered a medication error and should be coded as such.

a). False

b). True

Question: 5

Medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation is known as:

a). Abuse

b). Overdose

c) Off-label use

d). Misuse

Question: 6

In context of drug/medicinal product exposure during pregnancy, if mother experienced an ADR and fetal defect/ADR in baby have been reported, then

a). Two cases will be created: one for mother, one for baby

b). Only mother case will be created

c) Only baby case will be created

d). All above options are not correct

Question: 7

In context of drug/medicinal product exposure during pregnancy, if mother experienced an ADR and fetal death without information on malformation have been reported, then

a). Two cases will be created: one for mother, one for baby

b). Only mother case will be created

c) Only baby case will be created

d). All above options are not correct

Question: 8

a). Lack of efficacy of a medicinal product is not considered a medication error per se.

b). There may be medication errors which lead to a lack of efficacy in the patient, for example where a patient has accidently received an underdose. The coding should reflect the error and include e.g. the PT Drug ineffective

c) Reports of ME with no associated suspected adverse reaction should not be submitted as ICSRs

d). All above options are not correct