Module 10: Medical Assessment of ICSRs

Introduction (1)

- Medical Assessment of an Individual case is performed after the case has undergone Data Entry and Quality Control check.
- The key aspects of the case that are reviewed during the Medical Assessment step are as follows:
  - Seriousness
  - Expectedness
  - Causality
  - Case Medical Information
  - Reportability Classification

Introduction (2)

The purpose of Medical Review is as follows:

- Confirm appropriateness of the AE terms selected.
- Confirmation of the seriousness classification of the AE terms.
- Agreement with the listedness/expectedness classification of AE terms.
- Agreement with outcome classification.
- Agreement with the coding of AEs, concomitant conditions, and medical history.
- Review of the narrative to ensure that it makes clinical sense and includes all important elements
- Authoring the company clinical comment, including determination of the company causality assessment, when appropriate.
- Identification of any specific additional information needed for medical assessment purposes other than routine follow-up requests required for case completion. Pursuit of follow-up on single case reports should be tailored according to the importance of the case in terms of attempts made and methods used (CIOMS, 2001).
- Consideration of ‘upgrade’ or ‘downgrade’ to the case’s regulatory reportability classification.
- Identification of potential safety signals.

SERIOUSNESS ASSESSMENT

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Serio**us Adverse Events**

- A serious adverse event (experience) or reaction is any untoward medical occurrence that (at any dose in case of clinical trials before marketing or at doses normally used in man in case of post marketing situations):

  - Results in death,
  - Is life-threatening,
  - Requires inpatient hospitalization or prolongation of existing hospitalization,
  - Results in persistent or significant disability/incapacity, or,
  - Is a congenital anomaly/birth defect
  - Is an Important Medical Event (IME)

SAE Criteria

Life threatening

- Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Hospitalization

- Visit to the emergency Room is not considered as ‘hospitalization’ to classify as a serious criterion. However, whether it would be assessed as serious will depend on the context of the case report.

SAE - Important Medical Event (IME) /Medically Significant Event

- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate for IMEs that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, but, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes documented in the bulleted list (for SAE)
- Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that to do not result in hospitalization; or development of drug dependency or drug abuse.
- Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

SAE - Medical/Surgical interventions

- Medical and surgical interventions provide important information as to the seriousness of a particular event, so they should be reviewed as part of the medical assessment. Examples of the impact of intervention on seriousness are as follows:

- Examples

1. Intravenous administration of medication would generally be consistent with treatment for a serious event.
2. Inhalation treatment or intramuscular medications administered in the hospital or emergency room would be consistent with treatment for a serious event, while HCP office or home treatment only would not generally be consistent with a serious event
3. Medications administered orally or topically would usually not be consistent with a serious event except if given sublingually

However, there could be exceptions to the above examples depending on the context of the case report.

SAE Criteria

- The MAH should **assess each event** for seriousness.
- When there is more than one reported event within a report, the MAH should **consider seriousness at both the event and case level**.
- It would be expected that a MAH takes a **conservative approach** in this scenario; that is, when an ICSR describes more than one event term, if any of the individual terms are assessed as serious, the case-level seriousness should be considered as serious.

EXPECTEDNESS ASSESSMENT

Expectedness

Synonyms

Listedness – For Events included in CCDS

Labelledness – For Events included in local labels (e.g. SmPC and USPI)

Expectedness?

Unexpected Adverse Reaction *An Adverse Reaction, the nature and severity of which is not consistent with the applicable product information or labeling*

- The concept of expectedness refers to events that may or may not have previously been observed and documented. Doesn't refer to what might be anticipated ("expected" in a literary sense) from known pharmacological properties of a drug
- An AR will be unexpected in the regulatory sense unless it is mentioned in the appropriate reference safety information (RSI) document(s) for the drug
- RSI may be one or more of the following: a component of an Investigator Brochure (Development Core Safety Information, e.g.), a company's core safety information (CCSI) within its internal core data sheet, or the official local data sheet (e.g., Package Insert in the US, Summary of Product Characteristics (SPC) in the EU).

Criteria for expectedness

- Event
- Preferred Term
- Seriousness
- Severity
- Specificity
- Outcome
- Event Level and Case Level

Expectedness Assessment Guidance

- A sign, symptom or diagnosis that already appears in the list of adverse reactions in an RSI is not classified as “unexpected” if reported using another term which has the same meaning

- A sign, symptom or diagnosis is not considered as “expected” when it is different from reactions already included in the RSI with respect to their nature, specificity, mechanism, severity, or outcome

- In the absence of sufficient documentation and in the face of uncertainty, a reaction should be regarded as unexpected.

Expectedness Assessment Guidance

*Further **anatomical** specification:*

- left-sided chest pain is equivalent to chest pain; it should not be assessed as unexpected if chest pain is expected
- If arteritis is expected, temporal arteritis should be considered unexpected due to the associated additional risks and poorer prognosis

*Further **histological** specification does* not *per se* make an expected ADR unexpected [e.g. a liver biopsy shows hepatic necrosis (expected) with the presence of eosinophils (not mentioned in labeling)

*Greater **diagnostic specification:*** Cerebral thromboembolism and cerebral vasculitis would both be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents

Expectedness Assessment Guidance

Further specification regarding ***severity***:

- Fulminant hepatitis should not be considered expected if “liver injury” is mentioned in the reference information; owing to the known high incidence of fatal outcome.
- If rash is listed, and SJS is reported, what is the assessment?
- If hepatitis is listed, and hepatic transaminases elevated is reported, what is the assessment?

Further specification regarding ***duration***:

- If the label refers to acute elevated liver function tests, a raised level lasting three months would be unexpected. Thus, prolonged cholestatic liver injury should not be considered expected when acute cholestatic liver injury is mentioned in the RSI, since prolonged forms may not be reversible.

Expectedness Assessment Guidance

Do additional signs and symptoms necessarily infer unexpectedness?

- Mention of any additional symptoms or signs usually associated with an expected ADR does not always merit upgrading the event to unexpected. Petechia associated with labeled thrombocytopenia (when petechia with thrombocytopenia is reported), or dehydration associated with labeled pseudomembranous colitis (when dehydration with pseudomembranous colitis), are not unexpected.

- If an expected ADR is not usually accompanied by or complicated by a sign, the ADR (i.e. the complication) should not be considered expected. Melena, a complication of labeled gastrointestinal irritation, is unexpected because gastrointestinal irritation per se does not usually cause bleeding. On the other hand, melena would be expected if the label includes “gastrointestinal bleeding.”

Expectedness Assessment Guidance *(Contd.)*

How should signs and symptoms of a diagnosis or syndrome be handled?

- If a diagnosis is an expected ADR, then it's signs and symptoms are also considered to be expected, when they are reported as associated. E.g. if anaphylactic reaction is labeled, then a report of hypotension, wheezing, and urticaria together would be expected event.
- The reverse is not true however; a diagnosis relating to a group of symptoms or signs which are each individually labeled would not usually be considered expected. A reported anaphylactic reaction is unexpected if only isolated hypotension/wheezing/urticaria are labeled.

Expectedness Assessment Guidance *(Contd.)*

How Should Various Sections of a Core Data Sheet or Other RSI Inter-relate with Regard to Safety Information?

- The existence of concurrent medical disorders or abnormalities may be given as a reason for a contraindication or precautions-for-use. This does not imply, that such concurrent conditions are ADRs, unless they are specifically mentioned as such in the adverse reaction section. If it is specified (for example in the dosing section of CCSI), that dosage should be reduced in case of renal insufficiency, then renal insufficiency is not an expected ADR unless it is also included in the ADR section

Expectedness Assessment Guidance *(Contd.)*

Events with FATAL outcome

- Unless the RSI specifies an event to be associated with fatal outcome, then the event should be considered unexpected
- If preexisting underlying disease progresses to death (e.g. fatal malignant neoplasm progression), it is usually considered expected
- Fatal cardio-respiratory arrest is considered expected if cardio-respiratory failure is listed

Expectedness Assessment Guidance *(Contd.)*

What is the Role, if any, of "Class Labeling" in RSI ?

- "Class ADRs" should not automatically be expected for the subject drug/suspect drug unless the drug itself is implicated

  Examples

  - Drugs of this class are known to cause tremors
  - Drugs of this class are known to cause tremors but no reports of tremors have been received till date with this drug
  - Drugs of this class including this drug are known to cause tremors

Expectedness Assessment Guidance *(Contd.)*

Should RSI Deal With Lack of Expected Clinical Effect?

- Lack of effect per se will not be written in the RSI
- If the treatment exacerbates the "target" disease (the indication for the medicinal product)

  Example: If the targeted indication (e.g. headache) exacerbates after taking drug X, the event should be considered unexpected
- An "unusual" lack of expected therapeutic effect for medicines used in life-threatening diseases, which may have life or death consequences. While individual reports are not per se unexpected, reports of unusual numbers of treatment failures may constitute a signal of a problem and should be handled as other changes in frequency are

Expectedness Assessment Guidance
(Contd.)

Overdose

- If an ADR is listed only under Overdose section, it should be considered unlabeled/unexpected if the ADR occurred at normal dose, but the reverse is not true.
- Overdose without any other ADR is usually considered as expected
- In case of overdose with associated ADRs, if all ADRs are labeled, overdose should be marked labeled
- If at least one ADR associated with overdose is unlabeled, overdose itself should be marked unlabeled

Note: Some companies mark overdose as labeled irrespective of listedness/labelling of associated ADRs

Expectedness Assessment Guidance
(Contd.)

Intentional overdose

- If patient has taken overdose of drug to commit suicide,
  - Patient was on the drug
  - Patient took somebody else's drug

- Suicidal ideation/intention, suicide attempt and completed suicide

Expectedness Assessment Guidance
(Contd.)

Labeling of Medication Errors

- Medication Errors with or without associated ADRs should be considered unlabeled
- Transmission of infectious agent/ contamination should be considered serious and unlabeled

Expectedness Assessment Guidance
(Contd.)

ADRs in CONTRAINDICATIONS section

- A medical condition mentioned as a contraindication for the drug should not be considered listed unless the medical condition is also mentioned in the ADR/Undesirable effects section
- E.g. In contraindications sections, if it is mentioned that the drug is contraindicated in patients with renal insufficiency and patient is reported to have renal failure, what is the assessment?

Expectedness Assessment Guidance
(Contd.)

ADRs in DRUG INTERACTIONS section

- If an ADR is reported to have occurred due to interaction between drug X and Y, the ADR should be considered if it is mentioned in undesirable effects section or in drug interactions section that ADR is reported to occur if X and Y are given together

- If an ADR is reported to have occurred due to interaction between drug X and Y (metabolized by CYP3A), and in drug interactions section it is mentioned that ADR is observed if X is given along with CYP3A inhibitors, ADR is labeled, although drug Y is not specifically mentioned

- No class effect – Only medical judgment

Expectedness Assessment Guidance *(Contd.)*

Sections to be referred for Expectedness Description

- Clinical Pharmacology – PK and PD
- ✓ **Black Box warnings**
- Special Precautions/Warnings/Contraindications
- Clinical Studies
- Indications and Usage
- ✓ **Adverse Reactions/ Undesirable Effects**
- ✓ **Drug Interactions**
- ✓ **Overdose**
- Information for Patients
- How Supplied – Dosage and Administration

CAUSALITY ASSESSMENT

Objectives of Causality Assessment

- To assess relationship between Drug and AE
- To monitor the safety profile of a drug
- Signal detection
- Regulatory requirement
- Case reporting
- To eliminate wrong conclusions and signals
- Direct resources at the true signals
- Update labeling information of the drug

Types of ADRs

Types of ADRs	Description	Examples
Type A: Most common type (80% of all ADRs)	-Direct extension of pharmacological action of drug -Dose related	-Hypoglycemia due to insulin -Hepatic necrosis due to paracetamol
Type B	-No relationship to the usual pharmacological effect of drug -Relatively uncommon; account for most drug fatalities -Difficult to predict -Not dose related, -Host dependent -Includes idiosyncratic reactions and drug allergies	-Drug induced rashes, -Increased vulnerability of erythrocytes to oxidative injury by several drugs in G6PD deficient individuals (Main goal of pharmacovigilance systems is to identify such effects as early as possible)

Types of ADRs *(contd.)*

Types of ADRs	Description	Examples
Type C	-Related to the duration of treatment and to some extent to the dose as well -Long-term exposure required	-Analgesic nephropathy -Tardive dyskinesia seen with antipsychotic medications
Type D	-Seen on prolonged exposure to drug or exposure at a critical time	-Increased risk of endometrial cancer with tamoxifen -Teratogenic potential of drugs
Type E	Seen on abrupt discontinuation of long-term therapy	-Delirium tremens on alcohol Withdrawal -Rebound hypertension on clonidine withdrawal

Factors in causality assessment

- Drug profile
  - Can the drug cause the AE?
  - Has the drug caused the AE?
  - Same problem earlier with same or similar drug?
- Patient profile:
  - Any other factors present in this patient?
  - Comorbid conditions
  - Co- suspects
- Disease course, Rx provided and outcome

Factors in causality assessment

- Time lag between drug use and AE occurrence (Temporal relation)
- Outcome after drug discontinuation
- Was the outcome affected by Rx administration
- De-challenge
- Re-challenge information

Causality Assessment Methods

- World Health Organization method
- Naranjo's ADR probability scale
- French imputation system
- European ABO system
- Bayesian system
- Jones scale
- Karch and Lasagna scale

Causality Assessment

- Causality assessments are made using an overall review of the case and using a set of questions as a tool to support causality assessment evaluations using the **TRENDS** approach:
- **T**emporal relationship - is there a time relationship between event and product?
- **R**e-challenge - what happens when the consumer is re-challenged with the product?
- **E**xclusion - have other factors been excluded, e.g., concomitant medications?
- **N**ovelty - has the reaction been described and reported before?
- **D**e-challenge - did the reaction improve when the product was withdrawn?
- **S**cientifically plausible - is the event biologically/pharmacologically plausible?

Causality Categorization by WHO-UMC

- Related/Certain - clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug (product) administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (product) (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
- Probable/Likely - clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug (product), unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
- Possible - A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug (product), but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug (product) withdrawal may be lacking or unclear.

Causality Categorization by WHO-UMC

- Not Related: There is no WHO-UMC category that corresponds to “Not related”, however, there will be instances when an AE is clearly not related to the suspected product and “not related” is the most appropriate choice. For example when the reporter states “not related” and the company medical assessment concurs with the reporter’s.
- Doubtful
- Unlikely - A clinical event, including laboratory test abnormality, with a temporal relationship which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations
- Conditional/Unclassified - A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
- Unassessable /Unclassified - A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

WHO–UMC causality assessment criteria

Categories	Time Sequence	Other drug/disease ruled out	Dechallenge	Rechallenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

Naranjo's ADR probability scale

Sr. No.	Questions	Yes	No	Don't know
1	Are there previous conclusive reports on this reaction?	+1	0	0
2	Did the ADR appear after the suspected drug was administered?	+2	-1	0
3	Did the ADR improve when the drug was discontinued?	+1	0	0
4	Did the ADR appear with re-challenge?	+2	-1	0
5	Are there alternative causes for the ADR?	-1	+2	0
6	Did the reaction appear when placebo was given?	-1	+1	0
7	Was the drug detected in blood at toxic levels?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10	Was the ADR confirmed by any objective evidence?	+1	0	0

SCORING FOR NARANJO's ALGORITHM

>8 = definite; 5-8 = probable; 1-4 = possible; 0 = doubtful

Spontaneous Reports

- The company causality will always **default to possible** for spontaneous reports and no further evaluation by the physician/medical reviewer is necessary.
- If follow-up from a HCP is obtained for a spontaneous consumer report, the **HCP assessment of causality will supersede the consumer's** report. That is, if a consumer states that an event was related, and the HCP reports that it was not, then the reporter causality will be changed (i.e., downgraded) to 'Not Related'. Conversely, if a consumer thinks an event is not related, but follow-up from a HCP indicates that the event is possibly related, the reporter causality will be changed (i.e., upgraded) to 'Possible'. Rationale: Medical opinion supersedes subjective lay opinion.

Solicited Reports

- For HCP solicited reports, the medical reviewer may assign a company causality assessment. However, because company causality determines reportability, the company assessment must not downgrade the HCP's assessment of the case from related (related, probable, or possible) to unrelated (not related or doubtful)
- . For example, if the HCP's assessment is Probable, the PVP's assessment may be Possible, Probable, or Related, but it may not be Doubtful or Not Related.
- If the reporter (HCP) causality is reported and entered as doubtful, company causality should be entered as doubtful or higher (not downgraded to not related).
- For non-HCP solicited reports (eg, report from a consumer), company causality can be different than reporter causality (eg, the consumer states "possible", but the company causality is "doubtful"). This should be documented in the case narrative

Study Reports

- For study reports, the medical reviewer/physician may assign a company causality assessment .However, because company causality determines reportability, the company assessment must not downgrade the investigator's assessment of the case from related (very likely, probable, or possible) to unrelated (not related or doubtful).
- For example, if the investigator's assessment is Probable, the medical reviewer’s assessment may be Possible, Probable, or Very Likely, but it may not be Doubtful or Not Related.
- Similarly, if the reporter causality is reported and entered as doubtful, company causality should be entered as doubtful or higher (not downgraded to not related).
- When an investigator does not provide a causality assessment, the medical reviewer may assign a company causality based on his/her judgment, but follow-up must be requested to obtain the missing investigator causality.

Case Medical Information

Medical Assessment of an Individual case also encompasses:

- Reviewing the source document and verifying the medical data entered in the case . This includes the event information, treatments received, medical history, concomitant medications, laboratory data and any relevant medical/hospital records.
- Verifying the identified events and reviewing the Coding verbatim events (MedDRA) dictionary and ensuring that the Lowest Level Term (LLT) is nearest possible match to the verbatim term.
- Reviewing the case narrative from a medical standpoint to confirm the chronological order of events, based on the information provided in the source document and ensure that the narrative includes all the information.
- Identification of any specific additional information needed for medical assessment purposes other than routine follow-up requests required for case completion.
- Consideration of ‘upgrade’ or ‘downgrade’ to the case’s regulatory reportability classification depending on medical judgment (seriousness, expectedness and causality).

Reportability Classification

- Certain serious adverse events (SAEs) must be reported to health authorities within stipulated times.
- Most countries use “calendar days” rather than “business or working days,”
- Some countries still retain different rules for local cases, but by and large, thanks to ICH, CIOMS, and common sense, most countries have standardized on the same timing, format, and content of expedited (also called “alert”) reports.
- Since a case may undergo upgrade’ or ‘downgrade’ depending on medical judgment, it impacts the reportability of a case and any such amendment in the case would need appropriate documentation in the comments field within the safety database.

Questions?

Thank you