Module 10 – Medical Assessment of Individual Case Safety Reports

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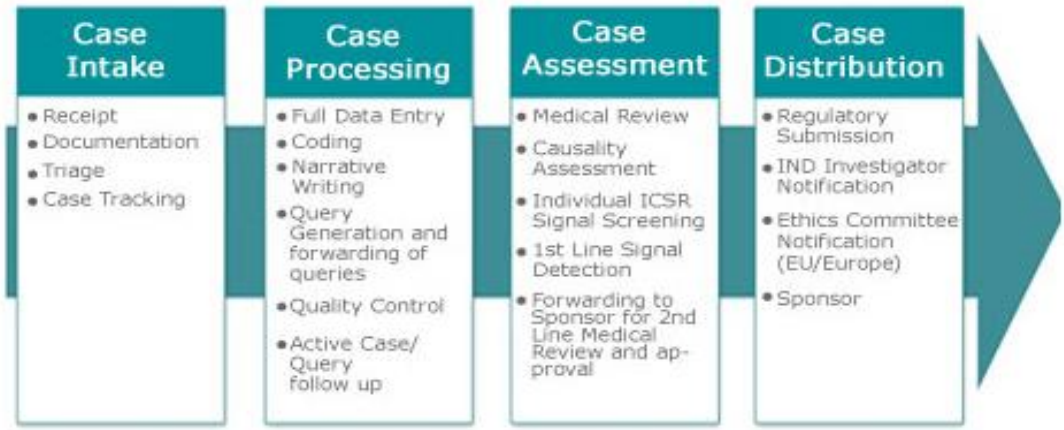
1. Introduction

The process of individual case processing involves the following steps: Case Intake, Case Processing, Medical Assessment and Distribution/Submission



Medical Assessment of an Individual case is performed after the case has undergone Data Entry and Quality Control check.

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.**

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

2. Seriousness

The generally accepted definition of seriousness is as follows:

A serious adverse event (experience) or serious adverse reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening ((NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect?

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition.

These should also usually be considered serious.

"Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse" (ICH E2A).

The European Union also notes that any suspected transmission via a medicinal product of an infectious agent is also considered serious.

Note that the FDA slightly altered the definition of "serious" effective March 2011 for clinical trials by adding the concept of "disability" directly into the definition, including the phrase: "substantial disruption of the ability to conduct normal life functions".

Over the years, these definitions have been discussed, parsed, and clarified by health agencies, companies, and other interested observers. In general, the most conservative interpretation is the one drug safety groups should use.

3. Expectedness

The United States regulations governing expectedness are straightforward:

For a pre-marketed product: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator's brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents (21CFR312.32(a)). FDA added to this definition effective March 2011 by noting in 21CFR312 that "Unexpected, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation." That is, an AE in the class labeling section of the brochure without specific mention for the study drug is considered unexpected.

For marketed products: Any adverse drug experience that is not listed in the current labeling (package insert or summary of product characteristics) for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. AEs that are "class-related" (i.e. allegedly seen with all products in this class of drugs) which are mentioned in the labeling (package insert or summary of product characteristics) or investigator brochure but which are not specifically described as occurring with this product are considered unexpected" (21CFR314.80(a)).

In the **European Union**, expectedness is addressed in Directive 2001/20/EC, which simply notes that an unexpected reaction is one "the nature or severity of which is not consistent

with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product)."

In theory, this concept is rather straightforward, but in practice, it becomes somewhat harder when synonyms and overlapping concepts are considered. In the report cited previously by Castle and Phillips, 72% of the European Union responders believed that if the labeled event is "dizziness," then "vertigo" would also be considered expected (labeled), but only 50% of the United States responders believed vertigo was labeled. Similarly, 18% of the European Union responders and 3% of the United States responders believed that if "hypotension, wheezing, and urticaria" are labeled, then a reported term of anaphylaxis would also be expected. Whether these differences persist, many years after the survey, is unclear.

However, it does highlight the fact that well-trained experienced medical personnel doing Pharmacovigilance can take the same set of facts and come up with differing and even opposing views.

Expectedness assessment based on the variety of Reference Safety information are technically split as follows:

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

In general, one should decide expectedness without thought to seriousness.

That is, just because a case is non-serious and the AE in question is mildly severe and of little medical import (e.g., a maculopapular rash) compared with a serious AE (e.g., severe hepatitis), the decision on expectedness should be made purely based on the wording in the label and not on the seriousness. Give each AE its due.

With clinical trial drugs, especially those not yet marketed, there may be minimal or no human experience (e.g., the first study in humans or the first phase II study after phase I studies that showed no AEs). In this case, there are no labeled events in the investigator brochure, and everything is thus "new" and unexpected. Anticipated events based on the pharmacologic

properties of the drug should not be considered expected until reported in a patient and put into the brochure.

In some cases, it is necessary to consider the route of administrations, dosage's, or indication's being studied when assessing the expectedness. This usually depends on how the investigator brochure or marketed labeling is written. Some describe a different set of AEs for different indications, dosages, or routes of administration. Care must be taken to apply the correct label to each case when doing expectedness.

Criteria for determining expectedness

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

Sections in Label to be referred for Expectedness Assessment

- 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

General guidance when assessing Expectedness:

- 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.

- Examples to Illustrate the Problems and Recommended Solutions

  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

  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.

▶ 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."

▶ 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.

▶ How Should Various Sections of a Core Data Sheet or Other RSI Containing Document Inter-relate with the regards to the 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.

▶ *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

▶ *What is the Role, if any, of "Class Labeling" in the 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*

▶ *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

▶ *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.

▶ *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

▶ *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

▶ *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?

▶ *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

The general advice would be, as with seriousness, to decide on the side of conservatism. Then, if there are questions on whether an AE is expected, consider it unexpected.

4. Causality

Of the three criteria revolving around the regulatory reportability of an individual case (seriousness, expectedness, and relatedness), this one is often the most difficult to do for the multiple reasons explained next.

Causality may be determined initially at the individual case level, after the receipt of an individual case safety report and again after the review of aggregate data in a case series as for signaling, risk management, and various regulatory reports, such as PSURs.

First, some basic "housekeeping" points should be cleared up to ensure that cases are always handled and collected in the same manner. In doing case assessment, one should be sure that cases are coded using the same MedDRA version and codes (some older dictionaries may still be used and some labeling for older drugs may not be in MedDRA), with trained coders who use consistent methodology and synonym lists. For aggregate reports, the search criteria for the case series should be complete and standardized (using searches from the MSSO and/or CIOMS). Where possible, Standardized MedDRA Queries (SMQs) should be used.

Cases should be followed up (rapidly upon receipt, not later) as appropriate to ensure the maximum amount of high-quality data.

In practice, many companies have two sets of standards and classifications for causality assessment of individual case safety reports. The first is used in clinical trials by the medical research group and the investigator (a separate causality assessment for each case should be done by the investigator and the sponsor as noted by FDA in the updating of the clinical trial regulations effective March 2011). The second is used in the drug safety unit. As there is no standard system, various categories (usually three to six) are used in case reports in clinical trials as follows:

- Related
- Probably related
- Possibly related
- Weakly related
- Unrelated

- Not assessable

This methodology is useful in later analyzing signals and in creating tables for investigator brochures, product labeling, and monographs to give a feel for the certainty or lack thereof about the causality of AEs by the drug in question. However, for the drug safety group, which has to determine whether a clinical trial case meets the three criteria (seriousness, expectedness, causality) for expedited reporting, the decision is **yes or no**. That is, the drug safety group must make the choice between unrelated and related. There is no middle ground or gray zone for causality here. Thus, the drug safety group has to make a rapid decision on whether the case is clearly unrelated (absolutely, positively) or everything else (possibly, probably, unlikely, weakly, etc.). Some drug safety groups consider "unlikely related" to be unrelated and other groups consider it in the broad "related" category.

Whichever way is decided, it should be made clear in writing in the SOP or working document (or the protocol for clinical trials) to everyone in the company what is done. Many drug safety officers believe that unless a case is clearly and absolutely unrelated, the causality should be, for reporting purposes, "related." To put it another way, the default causality for all cases is "possibly related" until there is evidence that the case is "unrelated." It is realized that this may not ultimately agree with the case analysis in the final clinical research study report, where a more nuanced opinion may be recorded. So, to summarize, in drug safety there are two causality choices for reporting purposes: unrelated (thus making the case not reportable as an expedited case) and everything else. Effective March 2011, the FDA changed the causality regulations, introducing the concept of "reasonable possibility" (21CFR32): Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. This wording changes the older concept of "possible association" to "reasonable possibility." It is not clear that this will make a major difference in practice.

4.1 WHO Criteria for causality assessment of ICSRs:

The WHO-UMC system has been developed in consultation with the National Centers participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognized that the semantics of the definitions are critical and that individual judgments may therefore differ. There are other algorithms that are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another.

The various causality categories are listed below.

Causality term Assessment criteria

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable/Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Conditional/Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

Unassessable/Unclassifiable

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

4.2 Hills Criteria of Causation

Hills Criteria of Causation outlines the minimal conditions needed to establish a causal relationship between two items. These criteria were originally presented by Austin Bradford Hill (1897-1991), a British medical statistician, as a way of determining the causal link between a specific factor (e.g., cigarette smoking) and a disease (such as emphysema or lung cancer).

Hill's Criteria form the basis of modern epidemiological research, which attempts to establish scientifically valid causal connections between potential disease agents and the many diseases that afflict humankind. While the criteria established by Hill (and elaborated by others) were developed as a research tool in the medical sciences, they are equally applicable

to sociology, anthropology and other social sciences, which attempt to establish causal relationships among social phenomena. Indeed, the principles set forth by Hill form the basis of evaluation used in all modern scientific research. While it is quite easy to claim that agent "A" (e.g., smoking) causes disease "B" (lung cancer), it is quite another matter to establish a meaningful, statistically valid connection between the two phenomena. It is just as necessary to ask if the claims made within the social and behavioral sciences live up to Hill's Criteria as it is to ask the question in epidemiology (which is also a social and behavioral science). While it is quite easy to claim that population growth causes poverty or that globalization causes underdevelopment in Third World countries, it is quite another thing to demonstrate scientifically that such causal relationships, in fact, exist. Hill's Criteria simply provides an additional valuable measure by which to evaluate the many theories and explanations proposed within the social sciences.

Hill's Criteria

Hills Criteria* are presented here as they have been applied in epidemiological research, followed by examples which illustrate how they would be applied to research in the social and behavioral sciences.

1. Temporal Relationship: Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must necessarily always precede the occurrence of the disease. This is the only absolutely essential criterion. This criterion negates the validity of all functional explanations used in the social sciences, including the functionalist explanations that dominated British social anthropology for so many years and the ecological functionalism that pervades much American cultural ecology.

2. Strength: This is defined by the size of the association as measured by appropriate statistical tests. The stronger the association, the more likely it is that the relation of "A" to "B" is causal. For example, the more highly correlated hypertension is with a high sodium diet, the stronger is the relation between sodium and hypertension.

3. Dose-Response Relationship: An increasing amount of exposure increases the risk. If a dose-response relationship is present, it is strong evidence for a causal relationship. However, as with specificity (see below), the absence of a dose-response relationship does

not rule out a causal relationship. A threshold may exist above which a relationship may develop. At the same time, if a specific factor is the cause of a disease, the incidence of the disease should decline when exposure to the factor is reduced or eliminated. An anthropological example of this would be the relationship between population growth and agricultural intensification. If population growth is a cause of agricultural intensification, then an increase in the size of a population within a given area should result in a commensurate increase in the amount of energy and resources invested in agricultural production. Conversely, when a population decrease occurs, we should see a commensurate reduction in the investment of energy and resources per acre. This is precisely what happened in Europe before and after the Black Plague. The same analogy can be applied to global temperatures. If increasing levels of CO2 in the atmosphere causes increasing global temperatures, then "other things being equal", we should see both a commensurate increase and a commensurate decrease in global temperatures following an increase or decrease respectively in CO2 levels in the atmosphere.

4. Consistency: The association is consistent when results are replicated in studies in different settings using different methods. That is, if a relationship is causal, we would expect to find it consistently in different studies and among different populations. This is why numerous experiments have to be done before meaningful statements can be made about the causal relationship between two or more factors. For example, it required thousands of highly technical studies of the relationship between cigarette smoking and cancer before a definitive conclusion could be made that cigarette smoking increases the risk of (but does not cause) cancer. Similarly, it would require numerous studies of the difference between male and female performance of specific behaviors by a number of different researchers and under a variety of different circumstances before a conclusion could be made regarding whether a gender difference exists in the performance of such behaviors.

5. Plausibility: The association agrees with currently accepted understanding of pathological processes. In other words, there needs to be some theoretical basis for positing an association between a vector and disease, or one social phenomenon and another. One may, by chance, discover a correlation between the price of bananas and the election of dog catchers in a particular community, but there is not likely to be any logical connection between the two phenomena. On the other hand, the discovery of a correlation between

population growth and the incidence of warfare among Yanomamo villages would fit well with ecological theories of conflict under conditions of increasing competition over resources. At the same time, research that disagrees with established theory is not necessarily false; it may, in fact, force a reconsideration of accepted beliefs and principles.

6. Consideration of Alternate Explanations: In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken other possible explanations into account and have effectively ruled out such alternate explanations. In other words, it is always necessary to consider multiple hypotheses before making conclusions about the causal relationship between any two items under investigation.

7. Experiment: The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen.

8. Specificity: This is established when a single putative cause produces a specific effect. This is considered by some to be the weakest of all the criteria. The diseases attributed to cigarette smoking, for example, do not meet this criteria. When specificity of an association is found, it provides additional support for a causal relationship. However, absence of specificity in no way negates a causal relationship. Because outcomes (be they the spread of a disease, the incidence of a specific human social behavior or changes in global temperature) are likely to have multiple factors influencing them, it is highly unlikely that we will find a one-to-one cause-effect relationship between two phenomena. Causality is most often multiple. Therefore, it is necessary to examine specific causal relationships within a larger systemic perspective.

9. Coherence: The association should be compatible with existing theory and knowledge. In other words, it is necessary to evaluate claims of causality within the context of the current state of knowledge within a given field and in related fields. What do we have to sacrifice about what we currently know in order to accept a particular claim of causality. What, for example, do we have to reject regarding our current knowledge in geography, physics, biology and anthropology in order to accept the Creationist claim that the world was created as described in the Bible a few thousand years ago? Similarly, how consistent are racist and sexist theories of intelligence with our current understanding of how genes work and how they are inherited from one generation to the next? However, as with the issue of plausibility,

research that disagrees with established theory and knowledge are not automatically false. They may, in fact, force a reconsideration of accepted beliefs and principles. All currently accepted theories, including Evolution, Relativity and non-Malthusian population ecology, were at one time new ideas that challenged orthodoxy. Thomas Kuhn has referred to such changes in accepted theories as "Paradigm Shifts".

4.3 Naranjo's ADR probability scale

The Naranjo algorithm, Naranjo Scale, or Naranjo Nomogram is a questionnaire designed by Naranjo et al. for determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding adverse drug reactions. It is also called the Naranjo Scale or Naranjo Score.

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

Definite: A reaction that:

- Followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues
- Followed a recognized response to the suspected drug and
- Was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

Probable: A reaction that:

- Followed a reasonable temporal sequence after a drug
- Followed a recognized response to the suspected drug
- Was confirmed by withdrawal but not by re- exposure to the drug and
- Could not be reasonably explained by the known characteristics of the patient's state.

Possible: A reaction that:

- Followed a temporal sequence after a drug
- Possibly followed a recognized pattern to the suspected drug and
- Could be explained by characteristics of the patient's disease

Doubtful: A reaction that was likely related to factors other than a drug

4.4 Uses and limitation of Causality Assessment

- What it can do?
    - Decrease disagreement between assessors
    - Classify uncertainty
    - Mark individual case reports
    - Improve the scientific basis of assessment.
- What it cannot do?
    - Give accurate quantitative measurement of the likelihood of a relationship
    - Distinguish valid form invalid cases
    - Quantify the contribution of a drug to the development of an adverse event
    - Change uncertainty to certainty

5. Case Medical Information

Medical Assessment of an Individual case also encompasses:

1. Reviewing the source document and verifying the medical data entered in the case against the source document. This includes the event information, treatments received, medical history, concomitant medications, laboratory data and any other relevant medical/hospital records.
2. Verifying the identified events in the case and reviewing the Coding verbatim events using a pre-determined medical dictionary, usually the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and ensuring that the Lowest Level Term (LLT) is nearest possible match to the verbatim term.
3. 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 provided in the source document.
4. 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).
5. Consideration of 'upgrade' or 'downgrade' to the case's regulatory reportability classification depending on medical judgment (seriousness, expectedness and causality).

6. 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,” as holidays and working days are not the same everywhere. 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.