

ISCR-MRCT

Causality Assessment Workshop for Clinical Trial Investigators



Topics To Be Covered

- Background
- Important definitions
- Distinction between cause & correlation
- Steps Involved in ADR diagnosis
- Causality Assessment by different stakeholders
- Common methodologies to assess causality
- WHO-UMC system
- Case studies

Let's start with the obvious

Adverse event reporting is essential to improving human subjects protections

The profile (efficacy, safety) is unknown before a pharmaceutical product is used

It is much much easier to determine causality in population studies using aggregate analyses

Background

- There is a definite need to develop understanding of causality assessment of adverse events in clinical trials to make objective judgment for better understanding of the safety profile of the molecule in question
- Numerous methods for causality assessment of adverse events have been published in the past
- Few have focused on the clinical trials perspective
- The WHO-UMC system of standardized case causality assessment provides a structure that can be applied to adverse events in clinical trials
- The Indian Society for Clinical Research (ISCR) has worked in collaboration with the Harvard Multi-Regional Clinical Trials (MRCT) Center to expand upon the WHO - UMC system and develop a comprehensive framework for clinical trials case causality assessment

Important Definitions

Adverse Events: Adverse event means any untoward medical occurrence that may appear during treatment with a pharmaceutical product (drug, biologic, vaccine, device) in humans, whether or not it has a causal relationship to the treatment.

Serious Adverse Events: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or disability or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect

Definition

In 1970, the World Health Organization (WHO) defined Adverse Drug Reaction (ADR) as:

Any response to a drug which is noxious, unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.” In common parlance, ADRs are also referred to as Adverse Events (AEs).

Important Definitions (2)

Adverse Drug Reactions:

- Anticipated (expected and predictable)
or
- Unanticipated (unexpected and unpredictable)

- Serious
or
- Not Serious

Side effect: Any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to the pharmacological properties of the drug. NOTE: The term “side effect” may only be used after the pharmaceutical product has been approved by the regulatory authorities.

Distinction between Cause & Correlation

The two fundamental questions about the causality are:

- 1) What is the evidence/information required for the legitimate conclusion of a cause and effect relationship?
- 2) What inferences can be drawn from such information/evidence and how?

Cause & Correlation

In practice, in both medicine and society:-

- the boundaries between cause and correlation are often blurred
- the word “cause” is often used somewhat loosely

However, while dealing with ADRs, the distinction between *cause* and *correlation* must be precise

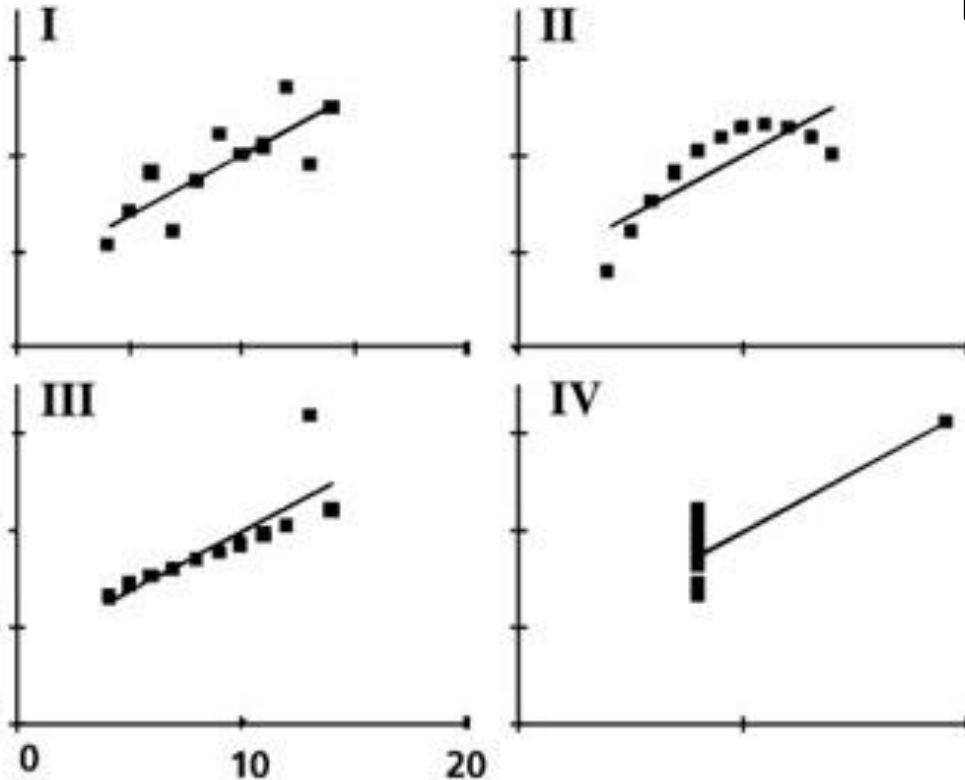
Cause: Something that produces an effect, result, or condition; something that makes something exist or happen: (if A, then B)

Correlation: A measure of a relationship between two random variables or two sets of data. NOTE: statistical dependence between two random variables is not sufficient to demonstrate causality. That is, “correlation does not imply causation.” Similarly, that does not mean that correlations cannot indicate the potential existence of causal relationships, but causes may be indirect and unknown.

Anscombe's Quartet

Each fictitious data set has:

- 11 (x,y) pairs
- Same mean of x values
- Same mean of y values
- Same regression coefficient
- Same variances
- Equation regression line ($y=3+0.5x$)
- Estimated standard error on regression coefficient



If possible, important to look at data graphically and not only by computational metrics

Distinction between Cause & Correlation

While assessing causality, following points need to be kept in mind:

- 1) Necessary and sufficient causes to trigger an adverse reaction
- 2) Pattern recognition

But also

- 1) Animal toxicology data
- 2) Detection of drug interactions
- 3) Potential contribution of “inactive” ingredients and formulations
- 4) Surveillance systems to compare safety profile of similar medications

Steps Involved in ADR Diagnosis

Standard steps include:

- obtaining history
- conducting appropriate physical examination & investigation
- using time as a diagnostic tool

Important Factors in ADRs

- 1) Temporal relationship (time to onset vs time drug was administered)
- 2) Nature of the reactions during this correlation (immediate vs long term)
- 3) Clinical and pathological features of the events
- 4) Existing information about the drug & same class of drugs
- 5) Concomitant medications
- 6) Underlying and concurrent illnesses
- 7) De-challenge or dose reduction
- 8) Re-challenge or dose increase – may not be possible/ ethical
- 9) Patient's characteristics & past medical history
- 10) Possibility of drug interactions

Complexities and Confounding Variables

- Availability of data
- Concomitant medications
- Drug interactions
- Non-drug therapies
- Diagnostic tests & procedures
- Underlying diseases & concurrent illnesses
- Common, spontaneous events - several commonly occurring ADRs (e.g. nausea, vomiting, diarrhea, rash, pruritus, drowsiness, insomnia to name a few) are also seen with perfectly healthy individuals/with placebo.
- Several studies have also documented increased reporting of symptoms when patients are specifically asked about such symptoms, as opposed to merely asking how they feel.
- The quality of information on the report

Preventable ADRs

- Medication errors
- Intentional abuse or misuse
- Unintentional misuse
- Intentional overdose
- Unintended or occupational exposure
- Drug quality problems

Right patient, right drug, right dose, right time,
right education, and right monitoring

Classification of ADRs

- **Type A (augmented):** exaggeration of drugs normal pharmacological actions when given at the usual therapeutic dose, normally dose-dependent. May include reactions not directly related to therapeutic action
- **Type B (bizarre):** novel responses unexpected from known pharmacological actions of the drug. Less common and may only be revealed after broad use
- **Type C (continuing):** persist for a long time
- **Type D (delayed):** become apparent after prolonged use of medicine. Timing of appearance may make detection difficult
- **Type E (end of use):** associated with the withdrawal of a drug

Causality Assessment by Different Stakeholders

Causality assessment by the prescribing doctor or investigator:

Causality assessment for all adverse events need to be conducted regardless of causation

Advantage: Investigator has detailed knowledge of the patient (current and past illnesses, concomitant medications, results of investigations)

Challenge: Investigators may not have been trained to assess causality for ADRs and may apply an incomplete, incorrect or inconsistent approach

Need for causality assessment by pharmaceutical company or regulatory authorities:

- Causality assessment for medically important, serious and expected reports is conducted to evaluate impact of causality on risk-benefit profile of the molecule

Common Methods to Assess Causality

These are generally classified in to three broad categories:-

1) Expert Judgments: These are individual assessments based on previous knowledge & experience

Challenge:

- No standardized tools to arrive at conclusions regarding causality
- Fails to achieve the level of reproducibility & validity required
- Lacks transparency
- Subjected to fallibility of human judgments (missing / misinterpretation of information)

2) Structured algorithms with or without scoring: Algorithms are set of specific questions with associated scores for calculating the likelihood of cause effect relationship.

Advantage:

- Transparent and consistent

Challenge:

- Reduced ability to apply clinical judgment
- Adherence to the scores in place of judgment with algorithms that include scoring

Common Methods to Assess Causality (Cont.)

3) Bayesian Approach: These use specific findings in a case to transform the prior estimate of probability into a posterior estimate of probability of drug causation.

- The prior information is calculated from epidemiological information and the posterior probability combines this back ground information with the evidence in the individual case to come up with an estimate of causation.

Due to problems of reproducibility and validity, no single method is universally accepted as the gold standard

Causality assessment

- Investigator or treating physician
- Research ethics committee
- Pharmaceutical company
- Regulatory authorities

WHO-UMC System for Causality Assessment

Methodology

- WHO-UMC model for causality assessment of an adverse event consists of:-
 - a framework which lists down 22 items of information
 - an assessment questionnaire with 29 binary-response questions
- The responses to the questionnaire can be plotted against essential and supplementary criteria for classification of an event into one of the 4 WHO-UMC causality categories:-
 - ‘certain’
 - ‘probable’
 - ‘possible’ &
 - ‘unlikely’
- A 5th ‘un-assessable / un-classifiable’ category is for cases with insufficient or contradictory information

No established system categorizes causality as “yes/no” due to obvious complexities and challenges

Information Gathering

- Table 1 on the next slide lists the information that will be required to appropriately analyze each adverse event
- Not all the 22 listed items will be needed for every event
- Against each listed item, Table 1 also suggests the source of that information
- While completing the causality assessment questionnaire presented as Table 2, it is recommended that users refer back to the corresponding items in Table 1

Table 1

Drug refers to the investigational product

No	Information to be Collated	Suggested Source
1.	Adverse event description: symptoms, signs, laboratory test results, pathological findings, etc.	Adverse Event Report and Follow-Up Reports
2.	Adverse event term or phrase that fits the event described under item #1.	Adverse Event Report and Follow Up Reports
3.	List of known adverse effects of the drug.*	Safety and Tolerability Section of the Investigator's Brochure
4.	Approved labels of other drugs of the same class.	Regulatory authority database.
5.	Description of mechanism of action and pharmacological actions of the drug.	Pharmacology Section of the Investigator's Brochure
6.	Date and time of last dose of drug before onset of event.	Patient history or hospital/clinic notes
7.	Pharmacokinetic parameters of the drug: time to peak plasma concentration; half-life.	Pharmacology Section of the Investigator's Brochure
8.	Date and time of onset of event.	Adverse Event Report and Follow-Up Reports
9.	Dose of drug, frequency, duration of continuous use till last dose before onset of event.	Prescription, hospital notes and patient history

Table 1

Drug refers to the investigational product

No	Information to be Collated	Suggested Source
10.	Name/description of underlying disease for which the patient was receiving the drug.	Hospital/clinic notes
11.	Any complications of underlying disease present at onset of event.	Hospital/clinic notes
12.	Concomitant illnesses the patient was suffering from at onset of event.	Hospital/clinic notes
13.	Duration of pregnancy at onset of event and EDD or actual delivery date, if applicable.	Hospital/clinic notes
14.	Cause of underlying physical/mental stress or injury, if any.	Patient history, hospital/clinic notes
15.	Surgeries in the past 3 months	Hospital/clinic notes
16.	Literature linking disease and background conditions to the event, if any.	Literature search through the Internet or other sources
17.	Concomitant medicines consumed by the patient within 7 days prior to onset of event.	Patient history, hospital/clinic notes
18.	Approved labels of concomitant medicines being taken by the patient.	Regulatory authority database

Table 1

*"Drug" refers to the investigational product

No.	Information to be Collated	Suggested Source
19.	Action and toxicity of traditional and alternative medicines being taken by the patient.	Literature search through the Internet or other sources
20.	Addiction history and use of recreational substances by the patient prior to onset of event.	Patient history, hospital/clinic notes
21.	Action, toxicity, and interactions of recreational substances used by the patient, if any.	Literature search through the Internet or other sources
22.	Post-event history: evolution of event; changes in therapy; treatment of event, with precise details.	Hospital/clinic notes

Table 1

No.	Information to be Collated	Suggested Source
1.	Adverse event description: symptoms, signs, laboratory test results, pathological findings, etc.	Adverse Event Report and Follow-Up Reports
2.	Adverse event term or phrase that fits the event described under item #1.	Adverse Event Report and Follow Up Reports
3.	List of known adverse effects of the drug.*	Safety and Tolerability Section of the Investigator's Brochure
4.	Approved labels of other drugs of the same class.	Regulatory authority database.
5.	Description of mechanism of action and pharmacological actions of the drug.	Pharmacology Section of the Investigator's Brochure
6.	Date and time of last dose of drug before onset of event.	Patient history or hospital/clinic notes
7.	Pharmacokinetic parameters of the drug: time to peak plasma concentration; half-life.	Pharmacology Section of the Investigator's Brochure
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9.	Dose of drug, frequency, duration of continuous use till last dose before onset of event.	Prescription, hospital notes and patient history
10.	Name/description of underlying disease for which the patient was receiving the drug.	Hospital/clinic notes
11.	Any complications of underlying disease present at onset of event.	Hospital/clinic notes
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*"Drug" refers to the investigational product

Causality Assessment Questionnaire

- Responses to 29 binary-response questions given in Table 2 presented in next two slides are the basis for an algorithm to aid in classification of an adverse event into one of the 4 working categories defined in the WHO-UMC system
- Ten of the questions are mandatory, while the rest may be applicable or not, depending on the responses to the mandatory questions
- Questions 1-7 to address drug-event relationship,
- Questions 8-19 to probe possibility of a non-drug cause for the event, and
- Questions 20-29 to investigate effects of de-challenge and re-challenge

Table 2

Q#	Question	T1 Ref*
1	<p>Is the drug or other drugs of the same class known to have this adverse effect?</p> <p>Guidance: <i>Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable information available on the drug.</i></p>	1-4
2	<p>If the answer to question 1 is "No", is the event consistent with the known pharmacological, toxicological or immunological action of the drug?</p> <p>Guidance: <i>Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable pharmacological information available on the drug.</i></p>	5
<u>3</u>	<p>Did the onset of the event occur within a reasonable time after the last dose of the drug to justify an association between the drug and the event?</p> <p>Guidance: <i>Consider the half-life of the drug and whether the drug persists within the body. Drugs are generally washed out of the body within 5-6 half-lives, but some drugs are known to persist in isolated compartments even after they are washed out from the blood. Sometimes, some drugs can trigger a pathological process that manifests itself long after the drug has been eliminated from the body - although this is extremely rare.</i></p>	6-8

Table 2 (2)

Q#	Question	T1 Ref*
4	<p>Was the event of acute nature that would be expected to correlate with circulating concentrations of the drug within the body?</p> <p>Guidance: <i>E.g., drug induced cardiac arrhythmia or convulsions are concentration dependent acute events while liver damage or pulmonary fibrosis are generally dose dependent.</i></p>	1-2
5	<p>If the answer to question 4 is "Yes", does the time of onset of the event correspond to a period when the plasma concentration of the drug is expected to be high?</p> <p>Guidance: <i>Consider the time to peak plasma concentration of the drug and its plasma half-life.</i></p>	6-8
<u>6</u>	<p>Does the event fit the description of a known pharmacological phenomenon (such as grey baby syndrome, tardive dyskinesia, or anaphylaxis)?</p>	1-2
<u>7</u>	<p>If the answer to question 6 is "Yes", is the dose, duration of therapy, and lag time prior to onset of event consistent with a causal relationship between the drug and the phenomenon?</p> <p>Guidance: <i>Base your judgment on descriptions of the phenomenon available in the literature.</i></p>	6-9

Table 2 (3)

Q#	Question	T1 Ref*
8	<p>Did the patient have an active disease or complication at the time of onset of the adverse event?</p> <p>Guidance: <i>Some clinical trial subjects, such as healthy volunteers in Phase 1 studies, and those participating trials of prophylactic agents such as vaccines, may not have an active disease at the time of onset of adverse event. In some patients the adverse event may be the first sign of an active disease.</i></p>	10-12
9	<p>Did the patient have an underlying physiological condition at the time of onset of the adverse event?</p> <p>Guidance: <i>E.g., pregnancy or puerperium.</i></p>	13
10	<p>Was the patient suffering from the effect of an underlying physical or mental stress or injury at the time of onset of the adverse event?</p>	14
11	<p>Was the patient recovering from a surgical procedure at the time of onset of the adverse event?</p> <p>Guidance: <i>Consider the duration of the healing process after surgery. Do not consider the effects of anesthesia for this point.</i></p>	15
<u>12</u>	<p>If answer to any question 8-11 is "Yes", is the disease, complication, condition, injury, stress or surgical procedure known to cause this AE? a</p> <p>Guidance: <i>Textbook references or any other credible reports of association between underlying state and event would be valid for a "Yes" response.</i></p>	16

Table 2 (4)

Q#		T1 Ref*
<u>13</u>	<p>If the answer to question 12 is "Yes", does it seem possible that the disease, complication, condition, injury or surgical procedure caused this adverse event? Guidance: <i>Consider whether the severity of underlying disease/injury, temporal sequence, and evolution of the event are consistent with a causal association. If your response to this question is "No", document the reason for ruling out the underlying state of the patient as cause for the event.</i></p>	16
14	<p>Was the patient known to be taking any concomitant medicines at the time of onset of the adverse event? Guidance: <i>Consider regular as well as intermittent or one-time use of concomitant medication. Include use of traditional and herbal medicine as well as other forms of alternative medicine and the effect of anesthetics in postoperative patients.</i></p>	17
<u>15</u>	<p>If the answer to question 14 is "Yes", are any of the concomitant medicines known to cause this adverse event? Guidance: <i>Refer approved prescribing information and any other literature available, for each of the concomitant medicines being taken by the patient.</i></p>	18-19
<u>16</u>	<p>If the answer to question 15 is "Yes", does it seem possible that one of the concomitant medicines known to cause this adverse event actually caused it? Guidance: <i>Consider whether the dose, duration of therapy, temporal sequence and half-life of the concomitant medicine was consistent with the time-course and severity of the event.</i></p>	18-19

Table 2 (5)

17	<p>Was the patient known to be taking any recreational substances at the time of onset of the adverse event?</p> <p>Guidance: <i>Include use of tobacco, alcohol, and abuse of prescription medicines as recreational use.</i></p>	20
<u>18</u>	<p>If the answer to question 17 is "Yes", are any of the recreational substances known to cause this adverse event?</p>	21
<u>19</u>	<p>If the answer to question 18 is "Yes", does it seem possible that any one of the recreational substances known to cause this adverse event actually caused it? Guidance: <i>Consider whether the extent of abuse and time sequence is consistent with a causal relationship of abuse to event.</i></p>	21
20	<p>Was the drug dose reduced or the drug withdrawn at any time after the onset of the adverse event?</p> <p>Guidance: <i>Enter "No" if, after the onset of the adverse event, the patient continued to receive the same dose of the drug at the same frequency as before onset of the event. Enter "Not Applicable" if the patient was expected to receive only one dose, or if the event occurred after the last scheduled dose of the drug, or if the patient died before the next dose could be given or before any effect of drug discontinuation can be expected (keeping drug half-life and reversal time of drug effects in mind).</i></p>	22

Table 2 (6)

21	<p>Was the dose of any of the concomitant medicines reduced or withdrawn at any time after the onset of the adverse event?</p> <p>Guidance: <i>Enter "Not Applicable" if the patient was not receiving any concomitant medicines at the time of onset of the adverse event.</i></p>	22
22	<p>Was the nature of the event such that withdrawal of the causative agent would be expected to lead to reduction/disappearance of manifestations in the days after withdrawal?</p> <p>Guidance: <i>Adverse events resulting from the direct pharmacological action of a drug are generally rapidly reversible, while recovery from effects of drug-induced injury to cells depends on the pace of regenerative processes in the affected tissue. Drug-induced degenerative changes and fibrosis may not be reversible. Choose your response based on the nature of the event and the withdrawal period that was available to observe the effect of drug withdrawal. You may choose "Not Applicable" if withdrawal was not possible.</i></p>	22
23	<p>If the answers to questions 20 and 21 are both "Yes", were the dose reductions/withdrawals of drug and concomitant medicines sequential?</p> <p>Guidance: <i>Enter "No" if one or more concomitant medicines were withdrawn (or their dose reduced) at the same time as withdrawal or dose reduction of the drug. Enter "Yes" only if there was sufficient gap between withdrawal of drug and the concomitant medicines to allow for a de-challenge effect to be observed for the drug and the concomitant medicine/s separately.</i></p>	22

Table 2 (7)

24	<p>If the answers to question 20, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on drug dose reduction/withdrawal?</p> <p>Guidance: <i>Confine your response to the effect of withdrawal or dose reduction of the drug, irrespective of the effect of withdrawal or dose reduction of concomitant medicines, and irrespective of whether withdrawals and dose reductions happened simultaneously or sequentially.</i></p>	22
25	<p>If the answers to question 21, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on concomitant medicine dose reduction/withdrawal?</p> <p>Guidance: <i>You need to respond to this question only if withdrawal or dose reduction of one or more concomitant medicines occurred sequential to withdrawal or dose reduction of the drug.</i></p>	22
26	<p>If the answer to question 24 or 25 is "Yes", are there any confounding factors that make the de-challenge results ambiguous?</p> <p>Guidance: <i>Specific treatment of a drug-related adverse event may confound the de-challenge results as both will reduce severity of the event.</i></p>	22

Table 2 (8)

27	If the answer to question 20 is "Yes", was the drug restarted after a period of withdrawal?	22
<u>28</u>	If the answers to questions 24 and 27 are both "Yes", did the manifestations of the event reappear after the drug was restarted?	22
29	If the answer to question 28 is "Yes", are there any confounding factors that make the re-challenge results ambiguous? Guidance: <i>A positive re-challenge result would be ambiguous if drug and concomitant medicines were restarted at the same time.</i>	22

- ❖ While the questionnaire has a total of 29 questions, classification to each category pivots on 6-7 or fewer crucial questions
- ❖ Generally, these are Q3, Q6-7, Q12-13, Q15-16, Q18-19, Q24, and Q28
- ❖ The remaining questions help validate answers to the key questions or may help tilt decision-making in favor or against the drug in cases of equipoise

Table 2

Q#	Question	T1 Ref*
1	Is the drug or other drugs of the same class known to have this adverse effect? Guidance: Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable information available on the drug.	1-4
2	If the answer to question 1 is "No", is the event consistent with the known pharmacological, toxicological or immunological action of the drug? Guidance: Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable pharmacological information available on the drug.	5
3	Did the onset of the event occur within a reasonable time after the last dose of the drug to justify an association between the drug and the event? Guidance: Consider the half-life of the drug and whether the drug persists within the body. Drugs are generally washed out of the body within 5-6 half-lives, but some drugs are known to persist in isolated compartments even after they are washed out from the blood. Sometimes, some drugs can trigger a pathological process that manifests itself long after the drug has been eliminated from the body - although this is extremely rare.	6-8
4	Was the event of acute nature that would be expected to correlate with circulating concentrations of the drug within the body? Guidance: E.g., drug induced cardiac arrhythmia or convulsions are concentration dependent acute events while liver damage or pulmonary fibrosis are generally dose dependent.	1-2
5	If the answer to question 4 is "Yes", does the time of onset of the event correspond to a period when the plasma concentration of the drug is expected to be high? Guidance: Consider the time to peak plasma concentration of the drug and its plasma half-life.	6-8
6	Does the event fit the description of a known pharmacological phenomenon (such as grey baby syndrome, tardive dyskinesia, or anaphylaxis)?	1-2
7	If the answer to question 6 is "Yes", is the dose, duration of therapy, and lag time prior to onset of event consistent with a causal relationship between the drug and the phenomenon? Guidance: Base your judgment on descriptions of the phenomenon available in the literature.	6-9
8	Did the patient have an active disease or complication at the time of onset of the adverse event? Guidance: Some clinical trial subjects, such as healthy volunteers in Phase 1 studies, and those participating trials of prophylactic agents such as vaccines, may not have an active disease at the time of onset of adverse event. In some patients the adverse event may be the first sign of an active disease.	10-12
9	Did the patient have an underlying physiological condition at the time of onset of the adverse event? Guidance: E.g., pregnancy or puerperium.	13
10	Was the patient suffering from the effect of an underlying physical or mental stress or injury at the time of onset of the adverse event?	14
11	Was the patient recovering from a surgical procedure at the time of onset of the adverse event? Guidance: Consider the duration of the healing process after surgery. Do not consider the effects of anesthesia for this point.	15
12	If the answer to questions 8, 9, 10, or 11 is "Yes", is the disease, complication, condition, injury, stress or surgical procedure known to cause this adverse event? Guidance: Textbook references or any other credible reports of association between underlying state and event would be valid for a "Yes" response.	16
13	If the answer to question 12 is "Yes", does it seem possible that the disease, complication, condition, injury or surgical procedure caused this adverse event? Guidance: Consider whether the severity of underlying disease/injury, temporal sequence, and evolution of the event are consistent with a causal association. If your response to this question is "No", document the reason for ruling out the underlying state of the patient as cause for the event.	16
14	Was the patient known to be taking any concomitant medicines at the time of onset of the adverse event? Guidance: Consider regular as well as intermittent or one-time use of concomitant medication. Include use of traditional and herbal medicine as well as other forms of alternative medicine and the effect of anesthetics in postoperative patients.	17
15	If the answer to question 14 is "Yes", are any of the concomitant medicines known to cause this adverse event? Guidance: Refer approved prescribing information and any other literature available, for each of the concomitant medicines being taken by the patient.	18-19
16	If the answer to question 15 is "Yes", does it seem possible that one of the concomitant medicines known to cause this adverse event actually caused it? Guidance: Consider whether the dose, duration of therapy, temporal sequence and half-life of the concomitant medicine was consistent with the time-course and severity of the event.	18-19

Continued on next page....

Table 2....Cont.

17	Was the patient known to be taking any recreational substances at the time of onset of the adverse event? Guidance: <i>Include use of tobacco, alcohol, and abuse of prescription medicines as recreational use.</i>	20
18	If the answer to question 17 is "Yes", are any of the recreational substances known to cause this adverse event?	21
19	If the answer to question 18 is "Yes", does it seem possible that any one of the recreational substances known to cause this adverse event actually caused it? Guidance: <i>Consider whether the extent of abuse and time sequence is consistent with a causal relationship of abuse to event.</i>	21
20	Was the drug dose reduced or the drug withdrawn at any time after the onset of the adverse event? Guidance: <i>Enter "No" if, after the onset of the adverse event, the patient continued to receive the same dose of the drug at the same frequency as before onset of the event. Enter "Not Applicable" if the patient was expected to receive only one dose, or if the event occurred after the last scheduled dose of the drug, or if the patient died before the next dose could be given or before any effect of drug discontinuation can be expected (keeping drug half-life and reversal time of drug effects in mind).</i>	22
21	Was the dose of any of the concomitant medicines reduced or withdrawn at any time after the onset of the adverse event? Guidance: <i>Enter "Not Applicable" if the patient was not receiving any concomitant medicines at the time of onset of the adverse event.</i>	22
22	Was the nature of the event such that withdrawal of the causative agent would be expected to lead to reduction/disappearance of manifestations in the days after withdrawal? Guidance: <i>Adverse events resulting from the direct pharmacological action of a drug are generally rapidly reversible, while recovery from effects of drug-induced injury to cells depends on the pace of regenerative processes in the affected tissue. Drug-induced degenerative changes and fibrosis may not be reversible. Choose your response based on the nature of the event and the withdrawal period that was available to observe the effect of drug withdrawal. You may choose "Not Applicable" if withdrawal was not possible.</i>	22
23	If the answers to questions 20 and 21 are both "Yes", were the dose reductions/withdrawals of drug and concomitant medicines sequential? Guidance: <i>Enter "No" if one or more concomitant medicines were withdrawn (or their dose reduced) at the same time as withdrawal or dose reduction of the drug. Enter "Yes" only if there was sufficient gap between withdrawal of drug and the concomitant medicines to allow for a de-challenge effect to be observed for the drug and the concomitant medicine/s separately.</i>	22
24	If the answers to question 20, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on drug dose reduction/withdrawal? Guidance: <i>Confine your response to the effect of withdrawal or dose reduction of the drug, irrespective of the effect of withdrawal or dose reduction of concomitant medicines, and irrespective of whether withdrawals and dose reductions happened simultaneously or sequentially.</i>	22
25	If the answers to question 21, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on concomitant medicine dose reduction/withdrawal? Guidance: <i>You need to respond to this question only if withdrawal or dose reduction of one or more concomitant medicines occurred sequential to withdrawal or dose reduction of the drug.</i>	22
26	If the answer to question 24 or 25 is "Yes", are there any confounding factors that make the de-challenge results ambiguous? Guidance: <i>Specific treatment of a drug-related adverse event may confound the de-challenge results as both will reduce severity of the event.</i>	22
27	If the answer to question 20 is "Yes", was the drug restarted after a period of withdrawal?	22
28	If the answers to questions 24 and 27 are both "Yes", did the manifestations of the event reappear after the drug was restarted?	22
29	If the answer to question 28 is "Yes", are there any confounding factors that make the re-challenge results ambiguous? Guidance: <i>A positive re-challenge result would be ambiguous if drug and concomitant medicines were restarted at the same time.</i>	22

*Corresponding Table 1 row numbers for reference

Interpretation of Responses

- Table 3 on the next slide provides a snapshot of the responses for each of the 4 WHO-UMC causality categories
- Against the corresponding question number from Table 2, responses favoring each category shown in (+) column and disqualifying responses shown in (-) column
- Notes (Rules) that follow Table 3 provide a stepped approach to event classification
- Users should first document their responses and then test responses against the requirements for each category, starting with the category that, at first glance, seems to fit best, but then also testing the immediately adjacent categories, and finally choosing the best fit category in line with the notes to Table 3

Table 3

Q#	Response Options			CERTAIN		PROBABLE		POSSIBLE		UNLIKELY	
				(+)	(-)	(+)	(-)	(+)	(-)	(+)	(+)
1	Y	N	-	Y							N
2	Y	N	-								N
3	Y	N	-	Y	N	Y	N	Y	N	N	Y
4	Y	N	-								
5	Y	N	B			Y/B	N				
6	Y	N	-	Y	N						
7	Y	N	B	Y	N						
8	Y	N	-								
9	Y	N	-								
10	Y	N	-								
11	Y	N	-								
12	Y	N	B	N/B	Y						
13	Y	N	B			N/B	Y	Y			Y
14	Y	N	-								
15	Y	N	B	N/B	Y						
16	Y	N	B			N/B	Y	Y			Y
17	Y	N	-								
18	Y	N	B	N/B	Y						
19	Y	N	B			N/B	Y	Y			Y
20	Y	N	NA								
21	Y	N	NA								
22	Y	N	NA								
23	Y	N	B								
24	Y	N	B	Y/B	N	Y/B	N				
25	Y	N	B	N/B	Y						
26	Y	N	B	N/B	Y	N/B	Y				
27	Y	N	B								
28	Y	N	B	Y/B	N						
29	Y	N	B	N/B							

Rules

To classify as CERTAIN

- Q6 and Q7 must be Y AND Q1 must be Y AND Q12, Q15 *and* Q18 must be N or B
OR
- Q6 and Q7 must be Y AND Q1 must be Y AND Q28 must be Y AND Q29 must be N

To classify as PROBABLE

- Q3 must be Y AND Q5 must be Y or B AND Q13, Q16 *and* Q19 must be N or B AND Q24 must be Y or B AND Q 26 must be N or B

To classify as POSSIBLE

- Q3 must be Y AND Q13, Q16 *or* Q19 must be Y

To classify as UNLIKELY

- Q3 must be N
OR
- Q1 *and* Q2 must be N AND Q13, Q16 *or* Q19 must be Y

Causality and Pharmacovigilance

- Importance of causality assessment for successful pharmacovigilance program
 - Drug monitoring
 - Adverse events of specific formulations
 - ADR reporting
 - Product surveillance
 - Post-marketing reviews
 - Regulatory reviews

Effective Pharmacovigilance and Surveillance Programs

- Size of database
- Accurate and complete reports
- Quality of ADR reports
- Timeliness of reports
- Analyzing individual ADRs for commonalities
- Distinguishing 'signals' from 'noise' or 'confounding variables'
- Regulatory oversight and unbiased decision-making
- Successful and timely communications

Relationship of causality to compensation

Compensation definition extremely broad (at this time). AEs thought to be “related to” the trial are, for example:

- (1) the failure of the experimental agent to have the desired effect
- (2) any harmful effect of a clinical trial procedure, even if the procedure was part of the standard of care for the condition
- (3) the worsening of a condition that could have been expected due to the natural history of the disease condition.

Compensation

The amendment clarifying expectations for compensation of clinical trial related injury or death states that compensation will be made for:

- (a) Adverse effect of investigational product(s)
- (b) Violation of the approved protocol, scientific misconduct or negligence by sponsor or its representative or the investigator
- (c) Failure of investigational product to provide intended therapeutic effect
- (d) Use of placebo in placebo-controlled trial
- (e) Adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol
- (f) For injury to child in utero because of the participation of parent in clinical trial
- (g) Any clinical trial procedures involved in the study

See Ministry of Health and Family Welfare. GSR 53(E). Central Drugs Standard Control Organization, India. 2013 Jan 30. Available from: [http://cdsco.nic.in/writereaddata/GSR%2053\(E\)%20dated%2030.01.2013.pdf](http://cdsco.nic.in/writereaddata/GSR%2053(E)%20dated%2030.01.2013.pdf).

Case Studies

Scenario 1

SAE Event: Total Hip Orthroplasty

- Female in a Relapsing Remitting Multiple Sclerosis (RRMS) study
- Subject diagnosed with Multiple Sclerosis (MS) in June 2011

Past history:

- Had pain right hip for 2 years and diagnosed to have osteoarthritis right hip
- History of trauma 2 years ago
- Had avascular necrosis of hip for 18 months before MS diagnosis
- No history of alcohol abuse
- Concomitant medication included: Intermittent steroids between 2003-2008

Event details:

- Enrolled in the study in June 2011
- Came for orthopedic consultation 6 months later
- Routine investigations done included urine culture which reported E coli
- Subject given antibiotics and asked to come for review after a week
- Subject admitted for surgery 2 weeks later; study monitor alerted
- Monitor said once subject hospitalised for surgery must be reported as SAE
- Surgery performed and patient discharged 10 days later

Outcome: SAE resolved on discharge

Causality assessment?

Scenario 2

SAE Event: Viral meningitis and Urinary tract infection

- 40 year old female in a Relapsing Remitting Multiple Sclerosis (RRMS) study
- Subject diagnosed with Multiple Sclerosis (MS) in June 2010

Past history:

- No history of diabetes or hypertension
- Allergy history not reported

Event details:

- Enrolled on study at diagnosis
- Reported to site on 7 mo later with history of fever with chills, headache and 3 days of neck stiffness
- Given anti-malarials but fever did not abate
- Chest x-ray, ECG, routine blood examination, urine routine, culture and sensitivity done
- Subject admitted for further evaluation with persistent neck stiffness; the possibility of meningitis was considered and LP was done
- CSF showed predominantly lymphocytes with mildly elevated protein – possibility of viral meningitis considered
- Urine culture was positive for E Coli, antibiotics given per sensitivity report
- Patient discharged and asked to stop all meds several days later

Outcome: SAE Resolved

Causality assessment?

Scenario 3

SAE Event: Carcinoma – right breast

- Case involved a 45 year old female in a Relapsing Remitting Multiple Sclerosis (RRMS) study
- Subject was diagnosed with Multiple Sclerosis (MS) in 2008

Past history:

- Patient had a past history of optic neuritis, neuropathic pain, anxiety, cholelithiasis and hypertension of unknown duration
- Concomitant medications included: Telma-H (hydrochlorothiazide, telmisartan), Arkamin (chlorodine hydrochloride) and baclofen
- Allergy history not reported, no relevant family history

Event Details:

- Enrolled in the study 3 years after RRMS diagnosis
- Subject felt a lump in the right breast with heaviness and pain 3 months later. A ultrasound revealed a space occupying lesion with axillary. A biopsy demonstrated invasive ductal carcinoma
- Subject stopped taking study drug at time of event
- Subject received regular chemotherapy for the event

Outcome:

- Subject died in 2 ½ years later

Causality assessment?

Scenario 4

SAE – Death

- Case involved a 66 year old female with acute coronary syndrome
- Drug – New drug XXX given orally once daily.

Event details

- A 66 year old female was enrolled Nov 2010 into an outcomes study assessing of major adverse cardiovascular events of Drug XXX versus placebo in subjects following acute coronary syndrome. Drug was stopped 7 months later. The sponsor requested closure of the study one month after as PI had left. At that time there were about 40-50 enrolled patients that required followup. The newly assigned PI asked the ethics committee, 10 months, to reopen the study solely for collection of long term survival data. The REC approved the request.

Outcome:

- All Subjects were contacted within two months to obtain survival information. One of the subject's relatives informed the investigator that the subject died 6 months prior of "natural causes". The study team requested that the relative send appropriate documents; no further documentation was received.

Causality assessment?

Scenario 5

SAE Event: Surgery - Total abdominal hysterectomy with bilateral salpingo-oophorectomy due to pelvic inflammatory disease with dysfunctional uterine bleeding

Case involved a 46 year old female presenting with epilepsy

Drug – new oral antiepileptic drug XXX

Event details

Subject enrolled into an open-label, multicentre, follow-up trial to evaluate the long term safety and efficacy of Drug XXX used as an adjunct to standard medications in subjects suffering from epilepsy. 11 months after starting the trial, the subject was seen at a local hospital with a 6 month history of dysmenorrhea, leukorrhea and abdominal pain. Ultrasound of the abdomen revealed pelvic inflammatory disease with dysfunctional uterine bleeding. The consulting gynaecologist recommended total abdominal hysterectomy with bilateral salpingo-oophorectomy. Surgery was performed successfully. Subject was hospitalised for 5 days and then discharged.

Outcome:

Surgery TAH with BSO, hospitalized and discharged

Causality assessment?

Scenario 6

SAE Event: Cerebrovascular accident (Hemiplegia)

Drug- XXX

Past History: 38 year old Male with type II diabetes mellitus

Event Details

The patient was enrolled in a double blind placebo-controlled trial of drug XXX for the treatment of type II diabetes mellitus.

One month later, the patient experienced left sided hemiplegia and was hospitalized. The blinded therapy was discontinued. Medical records were received for the patient three months thereafter. Review at the time showed:

A CT scan without contrast on day of presentation showed cerebral infarct in the right parietal region. Over the next 10 days, the patient was treated with mannitol, ceftriaxone, ranitidine, saline infusion, aspirin, and metochlopramide. After discharge he was prescribed ciprofloxacin, metronidazole, ranitidine, and aspirin. Labwork : Hb 11.8, TLC 9.3, DLC neutrophil 71, lymphocyte 21, monocyte 6.9, eosinophil 0.7, platelets 2.46, PCV 36.4, RBC 4.22, MCV 86.0, MCHC 32.9, PBF (Peripheral Blood Film) no parasite seen, platelet adequate, fasting blood sugar 98 mg/dL, blood urea 31.0 creatinine 0.5, sodium 140, potassium 3.01, bilirubin 0.8, SGOT 26, SGPT 45, total cholesterol 106.7, HDL 26.2, LDL 62, VLDL 18.5.

Other diagnostic studies included a chest x-ray which revealed bilateral aspiration pneumonitis, ECG: sinus tachycardia; echocardiogram: normal; neck doppler: suggestive of occlusion in right internal carotid artery.

The patient recovered from aspiration pneumonitis.

On review at three months, the patient reported that he was slightly ambulatory but required assistance to carry out his activities of daily living.

On two months later, the investigator was informed by a family member that the patient had a cerebrovascular accident resulting in death of the patient. No autopsy was performed.

Causality assessment?

What if:

- Drug XXX=
 - New anti-platelet drug
 - New statin
 - Mega doses of niacin
 - New herbal medicine
 - DPP IV inhibitor

Scenario 7

SAE Event: cardiac chest pain, resulting in death

- Case: 40 year old male patient with ankylosing spondylitis
- Drug : XXX

Event Details:

- The patient was randomized and placed on therapy with drug/placebo for ankylosing spondylitis
- The patient completed the 6 month study.
- Concomitant medications included calcium carbonate, atenolol, hydrochlorothiazide
- 4 days later etoricoxib was prescribed
- Another 4 days later, the patient experienced chest pain and within 30 minutes died at home. Autopsy was not performed and no death certificate was available. The primary investigator confirmed the death, but no further documentation. The primary investigator confirmed that there was no abnormal vital signs at the last study visit.

Outcome: Death

Causality assessment?

What if:

- Drug XXX=
 - New oral formulation of oxycodone for pain
 - New NSAID- COX 2 Inhibitor
 - Mega doses of Vitamin E
 - New herbal medicine
 - New anti-thrombotic medication thought to have vascular effect

Scenario 8

SAE Event: Right Breast Cancer

- 70 year old female with high CV risk presenting with acute coronary syndrome (ACS)
- Drug – simvastatin+ezetimibe
- Subject was diagnosed with right breast carcinoma in June 2012

Event Details:

- In 2010 pt. was placed on blinded study therapy for treatment of ACS
- Concomitant medications included Pantoprazole, metformin, metoprolol, mecobalamine, aminobenzoic acid, choline bitartarate, clopidogrel, grape seeds, inositol, lycopene
- The date of most recent dose of study medication prior to event of breast ca was one day prior to diagnosis of breast Ca. Advised surgery ASAP
- During preparatory investigations to the surgery – pt diagnosed with cardiac Ischemia
- Pt had an angiogram with two areas of stenosis, and proceeded to angioplasty 6 days later
- 4 months after angioplasty, surgery for breast Ca was performed

Causality assessment?

Scenario 9

SAE Event: Metastatic cholangioadenocarcinoma of liver

- 62 yr old male with high CV risk in a Type 2 Diabetes Mellitus study
- Drug – Oral Antidiabetic agent- DPP IV Inhibitor)
- Subject was diagnosed with Hepatocellular Carcinoma with metastasis in Oct 2013

Event details:

- Patient randomized on in Dec 2011
- Date of last site 18 months later
- Metastatic cholangioadeno carcinoma of liver detected 4 months after last study visit
- Patient died 2 months after diagnosis

Causality assessment?

Scenario 10

- **SAE event/term: Death due to unknown cause**

- 50's year old male patient with Stage IV non-small cell lung carcinoma with anemia of chronic disease
- No other significant medical history in the past

- **Event Details:**

- Enrolled in the trial and received first dose of chemotherapy (Carboplatin + Gemcitabine) as standard of care and investigational product (IP) (blinded, placebo controlled), ECOG = 1
- IP indicated for anemia of chronic disease
- Patient received second cycle of chemotherapy and second dose of IP as scheduled
- Apart from weakness (grade 1), subject had no other complaints during the visit, vital signs and investigations were normal, ECOG continued to be at one.
- On 8th day of cycle 2, patient came for the dose of gemcitabine. Apart from persistent weakness (grade 1) and slightly impaired air entry on the right side of lung, all other vitals and investigations continued to remain stable
- Approximately one week later, patient's son called to inform that his father died suddenly at home

Causality assessment?

Scenario 10(con't)

- According to his son, patient was well through the afternoon of this death, talking with his neighbors
 - Complained of dizziness, lay down on the bed to rest, and within minutes passed away
 - There was no apparent chest pain, breathlessness, vomiting, urinary incontinence, convulsions or any other signs of distress. No treatment could be provided
 - Autopsy was not performed
 - Concomitant medications: Becosules (Vit B'plex +C), ciprofloxacin, tramadol, ranitidine, betamethasone, domperidone, ondansetron, dicyclomine, Zamadol (paracetamol, tramadol), cremafin, granisetron hydrochloride, pantoprazole
- Outcome: Death

Scenario 11

- **SAE event/term: Brain metastasis, death due to unknown cause**
 - 50's year old woman with stage IIIa breast cancer
 - Concomitant illnesses: diabetes mellitus, hypertension
- **Event Details:**
 - Patient enrolled in the study and received standard of care for breast cancer
 - Investigational agent was indicated for prevention of bone metastasis (blinded, placebo controlled)
 - After two years on the trial, patient came to the site with complaints of headache and vomiting (both grade 2)
 - CT scan revealed multiple brain metastasis
 - Patient was hospitalized for 2 days, improved following treatment with mannitol and dexamethasone and was discharged
 - She was re-hospitalized a day later unconscious, seen by neurologist
 - Symptomatic and supportive care provided (pantoprazole, ondansetron, Augmentin, fosphenytoin, fluid replacement). Pt regained consciousness, but was disoriented. Her general condition improved and was discharged after two days.
 - Investigational agent was due to be given (on an every three month schedule) but discontinued
 - Patient died at home one week following her discharge presumptively secondary to disease progression and brain metastasis
 - No autopsy was performed.

Causality assessment?

Scenario 12

- **SAE event/term: Headache**
 - 60's year old woman with post menopausal osteoporosis
 - Concomitant illness: diabetes mellitus on oral hypoglycemic agents
- **Event Details:**
 - Patient enrolled in the trial for post menopausal osteoporosis (PMO)
 - Investigational product (blinded, placebo controlled) administered once a month for PMO
 - Approximately three months in the study, patient experienced mild head injury, was admitted to another medical facility and discharged with advice to take anti-epileptic medication
 - After one week, she came to the site complaining of persistent headache, dull aching type, associated with vomiting and loss of appetite
 - Vital signs – normal, no CT scan performed
 - Treatment: ondansetron, cloxacillin, actrapid human insulin, pantoprazole, tramadol, neurobion forte, ranitidine, sodium valproate, phenytoin, paracetamol
 - No further deterioration in neurological condition and was discharged after four days
- **Outcome: resolved**

Causality assessment?

Scenario 15

- **SAE event/term: Fatal myocardial infarction, atrial fibrillation**
 - 70's year old male with advanced NSCLC (stage IV) with anemia of chronic disease
 - No other significant medical history in the past
- **Event Details:**
 - Enrolled in the trial and received first dose of chemotherapy (Carboplatin + Gemcitabine) as standard of care and investigational (blinded, placebo controlled) for anemia of chronic disease
 - Approximately six weeks later, patient came to the site with left sided chest pain and left arm pain; patient was hospitalized in the ICU
 - Troponin T test was positive, other labs within normal limits
 - Diagnosis: myocardial infarction with atrial fibrillation
 - ICU management started. Medications included sorbitrate, ecosprin, Claxane, atorvastatin, clopidogrel, amiodarone, metoclopramide, tramadol, ranitidine
 - 18 hours later, the patient suddenly became unconscious, cardiac arrest, revived with CPR. Patient denied intubation and mechanical ventilator support
 - After one hour, patient suffered second cardiac arrest, and could not be revived with CPR.
 - No autopsy was performed.
 - Last dose of chemotherapy and blinded IP was approximately one week prior to the onset of the event
- **Outcome: Death**

Causality assessment?

Questions
Thank you

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