Clinical Research Professionals Certification Exam Prep Session #3
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ICH E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

E2A

Current *Step 4* version

dated 27 October 1994

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

- The Efficacy Guidelines are concerned with the design, conduct, safety and reporting of clinical trials
- E2A deals with clinical trials (not Post-approval Safety Data Management)
- Some definitions in E2A differ slightly from the definitions in the FDA/ DHHS regulations

ICH E2A Definitions and Standards for Expedited Reporting

- Defines
  - Adverse Event (or Adverse Experience)
  - Adverse Drug Reaction (ADR)
  - Unexpected ADR
  - Serious Adverse Event (or Serious ADR)
- Standards for Expedited Reporting
  - Single Cases of Serious, Unexpected ADRs
  - Fatal or Life-Threatening Unexpected ADRs: **7 days**
  - All Other Serious, Unexpected ADRs: **15 days**
  - Managing Blinded Therapy Cases
- Miscellaneous

Definition: Adverse Event (or Adverse Experience)

- Definition: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

- An adverse event (AE) can therefore be any *unfavourable* and *unintended* sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, *whether* or *not* considered related to the medicinal product.

Definition: Adverse Drug Reaction (ADR)

- Definition: In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

- The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Definition: Unexpected Adverse Drug Reaction (ADR)

- Definition: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

  - Severity (intensity): Knee pain (mild vs severe)
  - Nature: Knee pain (location of the pain)

Definition: Serious Adverse Event or Serious Adverse Drug Reaction (ADR)

- Definition: A serious adverse event (experience) or 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 which hypothetically might have caused death if it were more severe.
  - requires inpatient hospitalisation or prolongation of existing hospitalisation,
  - results in persistent or significant disability/incapacity, or
  - is a congenital anomaly/birth defect.

Other Considerations on Serious Adverse Event or Serious Adverse Drug Reaction (ADR)

- ‘Medical and scientific judgement 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 hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *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 hospitalisation; or development of drug dependency or drug abuse.’
- Difference between the FDA regulations and the ICH E2A on Serious Adverse Event ‘FDA: …**and** may require **medical or surgical** intervention…’

Definition: Expectedness of an Adverse Drug Reaction

- The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:
  - 1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. (See section III.F. and ICH Guideline for the Investigator's Brochure.)
  - 2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Which of the following is a key component of a safety specification?

- A. The frequency of adverse events
- B. The severity of adverse events
- C. The timing of adverse events
- D. All of the above

An adverse event that is not a serious adverse event is one which (check all options that may apply)

- ❑ A. causes a disability
- ❑ B. is temporally associated with drug
- ❑ C. is not necessarily causally related to drug
- ❑ D. is life threatening

A participant in a clinical trial for treatment of joint pain developed a cough, severe sore throat, runny nose and fatigue a few days after receiving the study drug. The participant also tested positive for influenza A virus at a time when the seasonal flu is widespread. This event is most likely classified as

- A. An adverse event
- B. An adverse drug reaction
- C. An unexpected adverse drug reaction
- D. A serious adverse event

Which of the following is an unexpected adverse event? (check all options that may apply)

- ❑ A. A report of interstitial nephritis in a patient with acute renal failure listed as an expected adverse event in the investigator's brochure (IB)
- ❑ B. An event that is listed in the IB
- ❑ C. A report of fulminant hepatitis in a patient with hepatitis listed as an expected adverse event in the IB
- ❑ D. Any events that happen immediately after drug administration

Standards for Expedited Reporting (1)

- What Should be Reported?
- 1. Single Cases of Serious, Unexpected ADRs
  - All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) should always be specified.

Causality Assessment

- Required for clinical investigations cases.
- Health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.
- No standard international nomenclature.
  - The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.
- For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

Standards for Expedited Reporting (2)

- 2. Other Observations. There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate
  - For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
  - A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
  - A major safety finding from a newly completed animal study (such as carcinogenicity).

Reporting Time Frames

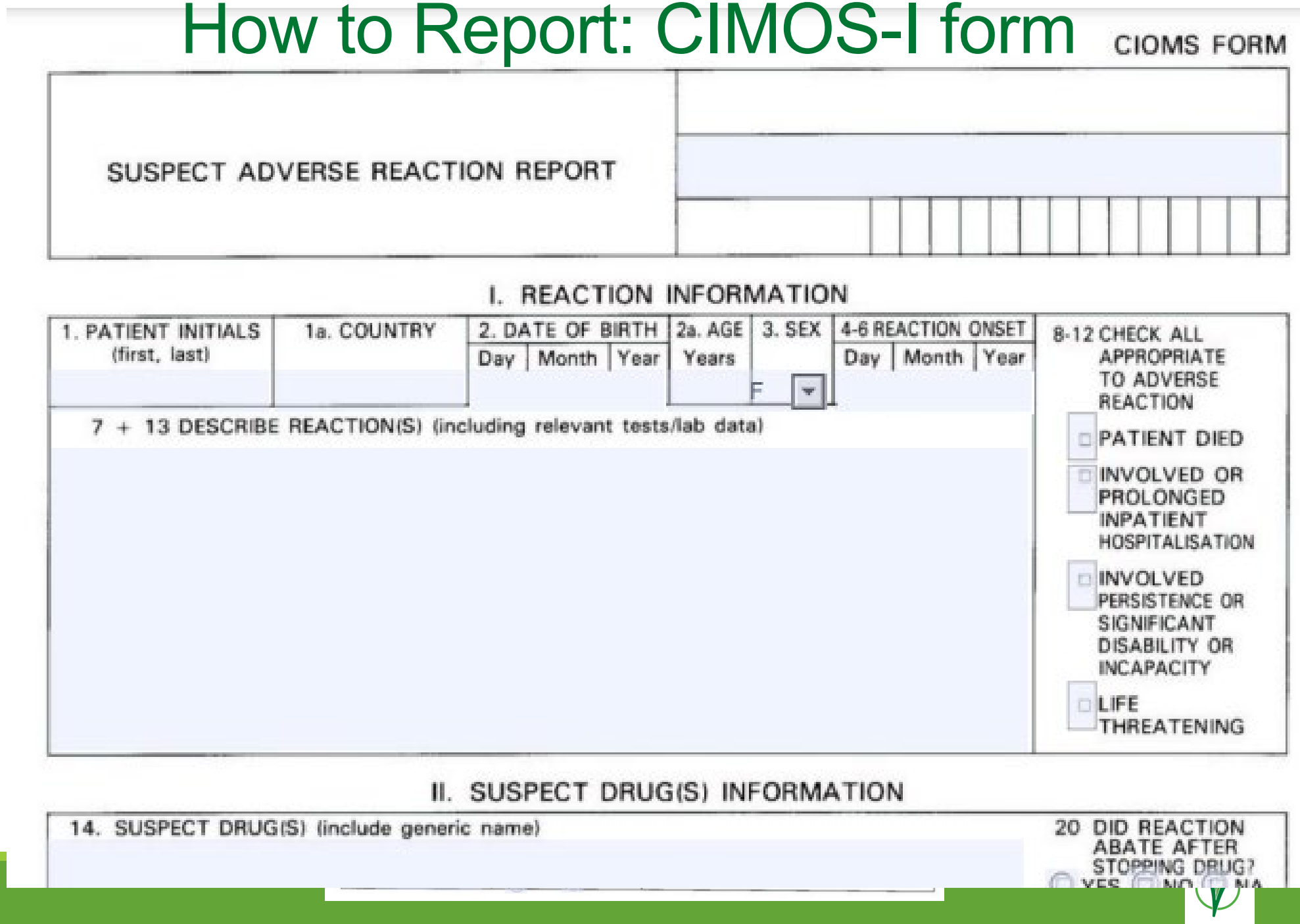
- Fatal or Life-Threatening Unexpected ADRs
  - no later than **7 calendar days** after first knowledge by the sponsor that a case qualifies,
  - followed by as complete a report as possible within **8 additional calendar days**.

- All Other Serious, Unexpected ADRs
  - no later than **15 calendar days** after first knowledge by the sponsor

Standards for Expedited Reporting (3)

- 3. Minimum Criteria for Reporting
  - An identifiable patient
  - A suspect medicinal product;
  - An identifiable reporting source;
  - An event or outcome that can be identified as serious and unexpected
  - For clinical investigation cases, there is a reasonable suspected causal relationship

How to Report: CIMOS-I form



CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day / Month / Year	2a. AGE Years	3. SEX F	4-6 REACTION ONSET Day / Month / Year

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- PATIENT DIED
- INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

20 DID REACTION ABATE AFTER STOPPING DRUG?

Managing Blinded Therapy Cases

- When a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind.
- Recommended that the blind be maintained for those persons responsible for analysis and interpretation of results at the study's conclusion
- When a fatal or other "serious" outcome is the primary efficacy endpoint, it may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting

Misc: 1. Active Comparator or Placebo Treatment

- Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.
- The sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies.
- Sponsors must report such events to either the manufacturer of the active control or to appropriate regulatory agencies.

Misc: 2. Products with More than one Presentation or Use

- An ADR that qualifies for expedited reporting with one presentation of a product (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or referenced to regulatory filings across other product presentations and uses.
  - a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed

Miscellaneous: 3. Post-study Events

- Not routinely sought or collected by the sponsor
- Serious adverse events that occurred after the patient had completed a clinical study will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports.

Per the ICH efficacy guidelines, expedited reporting is appropriate for (check all options that may apply)

- ❑ A. An increased rate of occurrence in cardiac arrhythmia listed on the IB
- ❑ B. A lack of efficacy of Drug A in a clinical trial in treating intractable epilepsy (a seizure disorder in which a patient's seizures fail to come under control with treatment).
- ❑ C. A new safety consideration for Drug H resulting from a new animal study
- ❑ D. A participant of a clinical trial on hair loss tripped and suffered a fractured ankle on his way to the first research visit.

An event that is severe in nature

- A. Will always require expedited reporting
- B. Should be considered as a serious adverse event
- C. May not meet the definition of a serious adverse event
- D. Need not be reported to the sponsor if it is part of the disease condition

A serious adverse drug reaction that is not fatal nor life-threatening must be filed with regulatory agencies as soon as possible, but no later than “X number” of days of the researcher first learned of the event

- A. 7
- B. 8
- C. 10
- D. 15

Which of the following statement(s) is correct

- A. A serious adverse event describes the intensity of the medical event
- B. An unexpected adverse drug reaction is a reaction that happens immediately after drug administration
- C. Adverse drug reactions require expedited reporting
- D. None of the above

In a clinical trial involving lung transplant patients, hospitalization for up to 2 days is expected and is considered usual. A subject was hospitalized for 3 days after receiving the study drug. This event is best described as

- A. an adverse event
- B. an expected adverse drug reaction
- C. an unexpected serious adverse drug reaction
- D. None of the above

Questions?

Contact:

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Please help us continue our support for clinical and translational research by citing our grant number in relevant publications: National Center for Advancing Translational Science of the National Institutes of Health Award UL1TR003015/ KL2TR003016.