Adverse Event Reporting

Adverse Event vs Adverse Reaction

- An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical trial subject ,administered a medicinal product and which **does not necessarily have a causal relationship** with this treatment

- An **adverse reaction(AR)** is all untoward and unintended responses to an investigational medicinal product **related** to any dose administered

Ref: Article 2 (m), (n) of Directive 2001/20/EC

Serious Adverse Event

- A **serious adverse event (SAE)/serious adverse reaction (SAR)** is an AE/AR which;

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- *+ an important medical event/medically significant*

(Ref: Article 2 (o) of Directive 2001/20/EC, 3(15) of 'CT-3')

- *A medical or surgical intervention to prevent life threatening illness*

(meddev 2.7/3 and 90/385/EED and 90/42 EEC)

SUSAR

Suspected **Unexpected** **S**erious **A**dverse **R**eaction requires expedited reporting to the regulator

(Ref: Article 2 (o) of Directive 2001/20/EC, 3(15) of 'CT-3')

How do we know what to expect?

- Reference Safety Information
- Investigator Brochure
- AOR
- Development Safety Update Report (DSUR)

Attribution of Causality

- The expression `reasonable causal relationship' is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship" between the AE and the investigational agent (s)/intervention(ICH-GCP)

- AEs should be reported with one of five attributions to study drug / intervention:

1. Definite (Clearly Related)
2. Probable(Likely Related)
3. Possible(may be related)“
4. Unlikely (doubtfully related) and
5. Unrelated (is clearly not related)

****This is the Responsibility of a Physician/Investigator ******

Eaton and colleagues (2013) analyzed data from 11,909 toxicities on 38 phase I trials sponsored by the NCI

Found the rate of drug-related toxicity increased with dose

"unrelated" and "unlikely" related toxicities were considered "unrelated,"

when

"possibly," "probably," and "definitely" related toxicities were considered as "related."

They propose a simplified binary system of "related" versus "unrelated“ when assessing the attribution of adverse events (AE) to study drug(s)

What should the Investigator report to the Sponsor?

- SAEs to be reported immediately by investigator to sponsor (within 24 hours)
- Immediate report to be followed by detailed, written reports

&

- AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the protocol

Ref: Article 16(2) of Dir 2001/20/EC (as amended), 4.3 (28) (29) (31), 5(34) of 'CT-3'

- To ensure no confusion or misunderstanding of the difference between the terms "serious“ and "severe," which are not synonymous, the following note of clarification is provided

- The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

- This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.
- Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Ref: EMEA: NOTE FOR GUIDANCE ON CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING -CPMP/ICH/377/95

Patient Assessment

- Comprehensive Baseline Physical Exam and Comprehensive Medical History is essential
- R/N or R/A review the patient before the MD
- When does an adverse event start and end – EOT or End of the Trial?
- Tools to Use: CTC , Assessment/ source data collection forms- Terminology must be appropriate
- Laboratory Values: Clinically Significant: Non Clinically Significant.
- Records must be: Attributable/ Legible/ Contemporaneous/Original/Accurate/ Complete (ALCOAC)

Scenario

Patient assessment Kidney disease.

Screening	Haemoglobin	= 11.8 g/dL
Visit 7	Haemoglobin	= 10.4 g/dL

The patient was not symptomatic and no treatment was given.

Should this be recorded as an adverse event?

Same Patient- Kidney disease

Routine Iron levels were taken

Results Iron 5 umol/l (normal limit 12-31 umol/l)

Iron Studies were ordered

Is this an AE?

- Patient had a knee injection

On assessment 3 weeks later, his chest was all bruised and sore.

On questioning , the patient reported he was at a party ,fell and was prescribed oral pain killers .Although he was mobile , he couldn't run around and do things like usual.

The doctor documented 'chest pain'.

- Record this AE correctly.?

Activities

- Draft an Adverse Event Assessment Form
- Draft a Con Med Assessment Form
- Draft a Medical History Assessment Form

- Complete a Medical Assessment History – Assess, Record and Grade.

Scenarios

John ,the patient ,complains of mild nausea 8 hours after administration of an oral investigation medicinal product (IMP). According to the Investigator Brochure (IB) temporary mild to moderate nausea has been associated with the IMP.

- The incident is recorded at site as **an AE**
- Severity is classified as **Mild** and the relatedness is classified as **probably related**
- What are the reporting timelines for this event? **AE form to be completed but not immediately reportable within 24 hours to the sponsor**

- What action would you expect to be taken in relation to the patient continuing to take the IMP? **No action (continue medication as it was an anticipated event as per the Investigator Brochure and it didn't meet serious criteria)**

- Patient A has been taking an oral IMP daily for 5 days. His wife contacts the research facility to report that the patient was admitted to hospital with severe vomiting. He required anti-emetics and IV fluids and was kept overnight in hospital. According to the Investigator Brochure (IB) temporary mild to moderate nausea has been associated with the IMP.

- The incident is recorded at site as **an SAE**

- Severity is classified as **Severe** and the relatedness is classified as **Possibly/Probably Related**

- What are the reporting timelines for this event? **24 hours to sponsor**

- What action would you expect to be taken in relation to the patient continuing to take the IMP? **IMP temporarily stopped at least as the event was related and unexpected (depending on the PI and circumstances and protocol requirements there are variety of options as per the SAE form)**

- Patient B has been enrolled for a clinical trial of an IMP. She had bloods taken at her screening visit all of which were within limits. At her randomization visit the patient reports that she tripped and sprained her ankle since her last visit. The site staff contacted the patients GP who revealed she had a soft tissue injury and was treated with compression and analgesia. She did not require hospital attendance and has fully recovered.

- The incident is recorded at site as **an AE.**

- Severity is classified as **Mild/Moderate** and the relatedness is classified as **not related (subject has not had the IMP yet)**

- What are the reporting timelines for this event? **AE form to be completed but not immediately reportable within 24 hours to the sponsor**

- What action would you expect to be taken in relation to the patient continuing to take the IMP? **No action taken, there was no IMP administered at time of event. No contraindication to randomization so patient would be randomized.**

Patient C suffers from hypertension and has been taking part in a clinical trial of a novel anti-hypertensive medication for 9 months. His blood pressure has been stable throughout participation in the trial. In the Investigator Brochure, dizziness & weakness appear as expected side effects of the IMP. At a scheduled visit the patient reports that he slipped on ice and fell, causing a fracture to his arm 2 weeks before. He was hospitalized for treatment for 2 days and his arm is in a Plaster of Paris and a sling.

The incident is recorded at site as **an SAE**. Severity is classified as **Moderate/severe** and the relatedness is classified as **possibly related**

What are the reporting timelines for this event? **24 hours to Sponsor**

What action would you expect to be taken in relation to the patient continuing to take the IMP? **No action because the SAE occurred 2wks previously and patient's BP has been stable throughout. (investigator may conduct further investigation i.e 24hr BP monitor and review the patient earlier than the next scheduled study visit).**

Patient D has a history of cardiac disease and is taking part in a placebo-controlled trial of an anti-thrombotic agent in addition to standard therapy. He is admitted to hospital and is diagnosed with a stroke. To facilitate treatment he is urgently un-blinded and is shown to be taking placebo.

The incident is recorded at site as **an SAE**

Severity is classified as **Moderate/Severe** and the relatedness is classified as **not related**

What are the reporting timelines for this event? **24 hours to sponsor**

What action would you expect to be taken in relation to the patient continuing to take the IMP? **Permanently discontinued**