Introduction to Collecting and Reporting Adverse Events in Clinical Research

Contents

Course Objectives and Contents

Objectives

Upon completion of this course, you will have an understanding of:

- The importance of collecting, recording and reporting adverse events;
- The definition for the different categories of adverse events;
- The mechanisms used for identifying these events, how they are evaluated when they occur and how follow-up may be carried out;
- The necessity of assessing a causal relationship between the study intervention and the adverse event; and
- What data is typically reported and who receives the reports.

Contents

- Introduction
- Why Adverse Events Should be Recorded
- What Should be Recorded
- Types of Adverse Event
- Detecting Adverse Events
- Collecting and Recording Adverse Event Data
- Adverse Event Evaluation
- Adverse Event Follow-up

- Assessment of Causal Relationship
- Unblinding
- Reporting Requirements
- Scenarios: Is it an Adverse Event, Serious Adverse Event or Neither

- Key Points to Remember

This section provides a summary of the key learning points of the course.

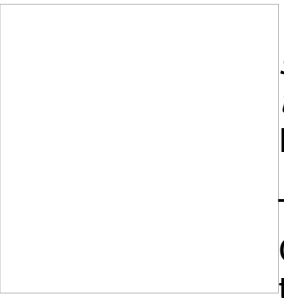
- References, Resources and Tools

This section provides the references used in this course and resources and tools which you may find useful for further information.

- Quiz

This section provides questions that will allow you to test what you have learned from the course.

Introduction



'An adverse event (AE) is any type of undesirable medical event (for example a sign or symptom or laboratory finding or disease) which is temporally linked to the investigational intervention and may or may not be caused by it' (Global Health Trials Glossary, 2011).

The International Conference on Harmonisation's Good Clinical Practice (ICH GCP) guidelines (1996) and regulators uses the term 'adverse event' in relation to medicinal products only, as it is derived from the safety monitoring of pharmaceuticals (pharmacovigilance), but it might also be applicable to other interventions in clinical trials.

Friedman et al. (2010) stress that the *'collection of adverse event data in clinical trials is a regulatory requirement and additionally, clinically and scientifically important. The challenge is to know what and how to collect these data, the frequency of collection and how to deal with small numbers of serious events'.* Guidelines from international organisations such as the World Health Organization (WHO), ICH and the Council for International Organizations of Medical Sciences (CIOMS) instruct that adverse events are carefully and systematically recorded.

Why Adverse Events Should be Recorded

Liu & Davis (2010) explain that AEs are collected in clinical trials on medicinal products to:

- Determine the safety profile of an investigational medicinal product (IMP)
- Evaluate any benefits and risks of the IMP
- Provide data for the package insert if the IMP is approved for marketing

They state that an IMP's safety profile '*is carefully monitored in clinical trials to determine whether there are any significant concerns that would prevent the product or test article from being used in its intended population'*. Safety data in the development of an IMP are recorded in the Investigator's Brochure. Occasionally IMPs are effective but further studies are discontinued due to serious adverse reactions.

As Loke & Derry (2001) state '*decisions on treatment are guided, not only by the potential for benefit, but also by the nature and severity of adverse drug reactions*'.

What Should be Recorded

Various methods are used to collect safety data and these can include: brief descriptions of AEs and detailed of SAEs seen in the participants. It is essential, when planning a trial, to fully understand and meet the requirements of the local regulatory authorities, the ethics committees, the sponsor of the trial and other stakeholders with regards to documenting and reporting AEs. Whichever system is used to collect and record AE data, it is important that it is consistent. If AE data is not documented in a systematic way and in sufficient detail, meaningful analysis may not be possible.

Particularly in a blinded study it is important to keep the balance between assuring the safety of participants and maintaining scientific integrity in an on-going trial. Interim analysis of unblinded AE data should therefore be carried out by either an independent Data Monitoring Committee or an independent qualified person responsible for pharmacovigilance at the sponsor's site. In such a case the trial needs procedures to ensure that members of the trial team are not unblinded.

The trial protocol should outline what is, for the purpose of the study, considered to be an adverse event, how these should be monitored, how and when they should be collected and recorded, what actions are to be taken, how and when it should be reported, etc. The revised CONSORT statement (2010) recommends only that '*All important harms or unintended effects in each group'* are reported.

What Should be Recorded

Loke & Derry (2001) point out two particularly important aspects of reporting which are:

- *adverse event recording in trials may frequently include unfavourable outcomes that arise from disease progression or concomitant co-morbidity, and are unrelated to drug treatment. Trial reports of adverse events need to make it clear which ones are thought to be adverse drug reactions (ADRs).*
- *different methods of recording ADRs can lead to significantly different results. For example, Olsen et al.'s study of hypertensive patients showed that rates of ADRs varied depending on whether spontaneous reporting, general enquiry, or specific questioning had been used.*

It is therefore vital that a practical and thorough system of collection and documenting these events is used throughout the trial.

Using the correct terms to describe AEs is important so that the data can be dealt with effectively and compared to others. There are 1100 preferred terms for drug AEs in the WHO's terminology system. For regulatory purposes the Medical Dictionary for Regulatory Activities (MedDRA) is used. This is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines). Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products.

Loke & Derry emphases the importance of using precise definitions '*although deviations from a precise definition of the term "adverse drug reaction (ADR)" may seem to be a minor issue, closer analysis reveals how misleading conclusions may result from the inappropriate use of terminology. A systematic review of postoperative analgesia found piroxicam to have a significantly better safety profile than placebo. However, on closer examination, we found that symptoms such as fever and headache were recorded as adverse effects in the piroxicam trials. Piroxicam is an effective treatment for fevers and headaches, and it is therefore no surprise that placebo turned out to have a greater rate of "adverse effects" and was considered less safe.*

Types of Adverse Event

As already described, an Adverse Event (AE) is any type of an untoward medical event

temporarily linked to the investigational intervention and may or may not be caused by it. Hackshaw (2009) explains that, in investigational medicinal product (IMP) trials, '*when it is judged that the event is likely to be caused by the intervention it can be called an 'adverse reaction' or 'adverse drug reaction'*

An adverse reaction/adverse drug reaction (AR/ADR) is an AE that is, in the opinion of a physician, causally related to an IMP (or a trial intervention) and could be the occurrence of a disease or condition (not normally the disease or condition being investigated) that directly affects the participant's health, safety or well-being.

According to the ICH-GCP Guideline and ADR is an AE of which the causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

ARs can be expected or unexpected:

- Expected adverse reactions are the 'adverse events' that are known about the IMP and have already been documented. The trial protocol or Investigator's Brochure or in case of already marketed products the Summary of Product Characteristics should provide a list of these.

- Unexpected adverse reactions are unanticipated adverse events that are not consistent with the known, predicted possible effects of the intervention. They could be a laboratory finding, symptom or disease associated with the IMP or any trial procedure which have not previously been documented.

Also if the event is not reasonably expected due to the natural history and progression of the underlying disease, condition or population, it can be considered as an unexpected AE.

Whether expected or unexpected, an AE (or AR) can be further described as serious or non-serious.

Types of Adverse Event

A 'Serious Adverse Event' (SAE) is any AE (which may or may not be related to the intervention) that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

If there is at least a reasonable possibility (i.e., the relationship cannot be ruled out) that there is a causal relationship between the SAE and the medicinal product it is a 'Serious Adverse Reaction' (SAR).

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious reaction that is likely to be related to the product (relationship cannot be ruled out) and also not expected from this product. Hackshaw (2009) states that a '*SUSAR is the most important type of event and requires special processing. For IMP trials a sponsor must report a fatal or life-threatening SUSAR to the regulatory authority within seven days of being notified. If the SUSAR is not fatal or life threatening the regulatory authority must be informed within 15 days'*. However, be aware that local regulations may require different reporting time frames.

In addition to the well-defined SAEs there are also medical events that do not fulfil the criteria described above for a SAE, but need to be reported. These are so called Important Medical Events that:

- may jeopardise the participant and
- might require intervention to prevent a ‘serious’ one (e.g. allergic bronchospasm, convulsions, etc.).

Important medical events should follow the same requirements as SAEs.

Detecting Adverse Events

AEs can be detected in a variety of ways. These can include:

- Asking the participant about AEs in general or for certain AEs at a regular check-up or an arranged interview.
- Observing the participant for any ‘tell-tale’ signs e.g. in the case of a vaccine trial, checking the injection site for local reactions (reactogenicity).
- Taking measurements from the participant e.g. body temperature, diameter of local reaction, blood parameters, etc.
- Spontaneous/unsolicited reporting, where the participant (or their representative) contacts a member of the research team to report or complain about an AE.

Solicited AEs are those collected in organised schemes such as clinical trials. In clinical trials solicited adverse events can be described as those that are specifically looked for which might be:

- Expected local or systemic ARs (reactogenicity: the capacity to produce ARs [known to occur for the IMP or class] and in vaccines is the capacity to produce an immunological AR such as a local response [redness, swelling, itching, blistering, scaling, etc.] or a systemic response [fever, headache, etc.].
- AEs (expected or unexpected) that are of sufficient interest to be collected systematically (e.g. AEs described in another trial that the sponsor wants specifically look at).

Solicited AEs are to be assessed as all other AEs apart from local reactions that are usual assessed as related.

Collecting and Recording Adverse Event Data

The trial protocol will list when reporting and recording should start. This might be for:

- AEs which occur after informed consent is taken
- AEs which start after the administration of the IMP
- any AEs which may occur throughout the course of the trial

The protocol will also indicate the length of time that the safety data should be collected for. This could be from the first day of collection until the end of the trial, a defined follow-up period after start of collection or on specific days following administration of the product.

Precise instruction of the duration and methods to be used for the collection and documentation of SAEs should be provided in the protocol or related SOPs. Collecting and recording of SAEs may begin from the first day of the IMP administration until the trial’s end or may, depending on the nature of the trial, include SAEs occurring during a specific time period after the end of the trial.

Adverse Event Follow-up

Usually, the trial protocol will require to follow-up AEs and especially SAEs and will state the

desired time period for this.

AE follow-up could be until:

- the resolution or stabilisation of the sign, symptom or laboratory change
  and/or
- the end of the study
  or
- a non-study related causality is assigned (investigations may be carried out to help inform on causality)

IMP related AEs which persist at the end of the trial may be followed-up until resolution or stabilisation.

SAE follow-up might include:

- tracking the SAEs in all participants including those withdrawn due to an SAE until a resolution or stabilisation, or until the event is otherwise explained.

Pregnancies that occurred during the study period (from the date of signed informed consent until completion of the participant's completion of the study) are usually not considered as an AE, but they need to be systematically documented and should be followed up until delivery or discharge in case of miscarriage for evaluation of the outcome of the pregnancy and the causality in case of a SAE.

Adverse Event Grading

Every AE should be graded or assessed for severity. There are usually four grades:

- Grade 1 is defined as mild and/or easily tolerated
- Grade 2 is defined as moderate and/or interferes with usual activity
- Grade 3 is defined as severe, resulting in inability to work or carry out usual activity and may require hospitalisation
- Grade 4 is defined as potentially life threatening and might fulfil the criterion of a SAE.

Detailed grading scales are provided by e.g. the Food and Drug Administration (FDA) or the Division of Acquired Immunodeficiency Syndrome (DAIDS).

It is important to understand that a 'severe' AE is not the same as a 'serious' AE.

The term 'severe' refers to the intensity or severity of the AE (e.g. Grade 3 = Severe, inability to do usual activity), while the term 'serious' is based on the outcome or action criteria associated with the AE (e.g. life threatening, hospitalisation).

Adverse Event Grading

An adverse event can also be a laboratory value that is out of range. Normal laboratory values are values for healthy adult and adolescent population (provided by an assay, manufacturer or laboratory) that are in the range of acceptable limits. Ideally a normal range from a local population should be used, since textbook values are usually derived from US populations and can be different to developing country values. Out of range values mean any values below or above the acceptable limit. Every out of range value constitutes an AE in principle and must be explained. AE grading tables may define a grade based on how many times the Upper Limit of Normal (ULN) the measured value is.

Possible reasons for out of range values:

- False laboratory measurement (appropriate quality control measures should be in place to avoid this)

- Range not applicable to population (a problem when a drug has been tested, for example, in the developed world and is being administered in developing countries).
- Health problem indicated, in which case the clinical significance must be evaluated.

An out of range value is usually considered as ‘not clinically significant’ if the participant is without clinical evidence at the time of blood collection and at the next follow-up visit (if applicable). The value is clinically significant if it corresponds with a clinical picture (e.g. decreased haemoglobin in Malaria, etc.).

Assessment of Causal Relationship

Systemic AEs, whether expected or not and whether serious or not, needs to be assessed for causal relationship. The assessment should be based on:

- Time of occurrence
- Medical history (underlying diseases as alternative possible causes)
- Other medication or procedures
- Erroneous administration of product
- Other factors

In some cases the causal relationship can be assessed by a repeated occurrence of the event, and in some cases of non-serious AEs a deliberate re-challenge might be justified to establish the causal relationship of an event.

Unblinding

There are usually two recognised justifications for unblinding:

1. when a participant has experienced an AE and requires treatment which cannot be given without knowing the study arm
2. when the sponsor requiring the unblinding information to report a SUSAR to the regulatory authorities and ethics committee

In addition, unblinding can be indicated when a pregnancy occurs and the treatment needs to be known for further actions.

Unblinding procedures are study specific and should be clearly stated in detail in the protocol. Care should be taken to maintain the integrity of the trial, while not compromising on safety.

Reporting of Adverse Events

Mulay (2001) stresses that '*reporting SAEs is your highest priority after participant care*'.

Fedor et al. (2006) state that the Sponsor usually requires the following information when reporting an adverse event:

- Route, dose, date and time of administration of the investigational product
- Date of report to sponsor
- Nature of adverse event
- Date and time of onset of adverse event
- Duration of event
- Resolution (if applicable)
- Laboratory data

- Concomitant medications
- Investigator’s assessment of severity classification
- Investigator’s assessment of the relationship of the investigational product
- The details of the person reporting the adverse event
- Actions that were taken
- Follow-up information

A trial may require more detailed information to be collected on SAEs/SARs than on non-serious AEs.

SAEs (which include SARs and SUSARs) should be reported to the coordinator or principle investigator immediately. They in turn should report the incident to the sponsor within 24 hours of becoming aware of the event.

Reporting of Adverse Events

The Sponsor reports SUSARs to regulatory authorities within seven calendar days if fatal or life-threatening, and the relevant follow-up information subsequently within an additional eight days. Other SUSARs should be reported within 15 calendar days

Depending on the set-up of the trial the coordinator or principle investigator may send reports on the SAE in addition to

- Safety Monitor/ Data Safety Monitoring Board (DSMB)
- Ethics Committee
- Trial Steering Committee
- Others (e.g. Manufacturer, Collaborators, etc.)

Generally studies will only report serious, unexpected and possibly related events, to the DSMB, ethics committee and sponsor.

The protocol will give timelines for reporting AEs and SAEs, but SAEs should be reported to the coordinator or principle investigator and to the Sponsor or their delegated receiver immediately (within 24 hours) of becoming aware of the event.

The protocol should also give timelines for submission of follow-up reports, where relevant. AEs may be upgraded in terms of severity or seriousness (e.g. a hospitalised participant goes on to die) but should not usually be downgraded (unless an error was later discovered). Similarly causality may change once more information is available. It is important that multiple or sequential reports of an AE are identified as being the same event to allow accurate event rates to be calculated.

In addition to the Sponsor, Ethics Committee involved in the oversight of clinical trials will have their requirements how the investigational site and/or Sponsor should report safety data.

Other parties might be receivers of AE or SAE reports such as Local Safety Monitors, Data Monitoring Committee (DMC)/ Data Safety Monitoring Board (DSMB) or a Trial Steering Committee (TSC).

Scenario Questions: Adverse Event, Serious Adverse Event or Neither?

Scenario 1:

A patient gave consent and was entered into a trial yesterday. This morning the

patient took the first dose of study medication and felt “severely nauseated” shortly afterwards. The patient said she was “violently sick” about an hour later. Was this an adverse event, serious adverse event or neither?

Scenario 2:

A female patient, who gave consent and agreed to practice adequate contraception in accordance with the study protocol, began treatment with the trial drug three months ago. Last week, the patient reported that she had become pregnant. Was this an adverse event, serious adverse event or neither?

Scenario 3:

A patient entered a 6-week study comparing nicotine patch and nicotine patch plus weekly counselling for ‘initial-phase’ smoking cessation. One week after consenting to take part in the trial, the patient underwent elective repair of a hernia. The operation was planned to take place in eight weeks’ time, after the study, but a cancellation created the opportunity for earlier surgery, which the patient gratefully accepted. Was this an adverse event, serious adverse event or neither?

Scenario Answers: Adverse Event, Serious Adverse Event or Neither?

Scenario 1:

Answer: Adverse Event (probably an Adverse Reaction)

Scenario 2:

Answer: Neither, however this might be a protocol deviation that may need further investigation and follow-up for the outcome of the pregnancy, possibly including monitoring of the health of the infant.

Scenario 3:

Answer: Neither, the hernia was a pre-existing condition, the hospitalisation was pre-planned.

Example of Recording an Adverse Event

Example of recording an AE:

Participant ID |___|___|___|___|___| Participant's Initials |___|___|___| Sex |___| (m/f)

ADVERSE EVENTS FORM

AE#	Report date *(DD/MM/YYYY)*	Description of adverse event	Event onset date *(DD/ MM/YYYY)*	Event end date *(DD/ MM/YYYY)*	Severity (Grade)	Relation-ship *	Action	Outcome	Reported as SAE	Indicate which AE is considered related to
	____/____/____		____/____/____	____/____/____						
	____/____/____		____/____/____	____/____/____						
	____/____/____		____/____/____	____/____/____						
	____/____/____		____/____/____	____/____/____						
	____/____/____		____/____/____	____/____/____						
	____/____/____		____/____/____	____/____/____						
	____/____/____		____/____/____	____/____/____						

Relationship is attributed by a physician. All local AEs are causally related to vaccination

Relationship to vaccine administration	Grade	Action	Outcome	Reported as SAE
0 = Not related 1 = Unlikely related 2 = Possibly related 3 = Probably related 4 = Definitely related.	1 = Present but easily tolerated 2 = Interferes with daily activities 3 = Prevents from daily activities 4 = Life-threatening, patients at risk of death (Report as SAE)	0 = No action taken 1 = Medication 2 = Non- Drug therapy 3 = Hospitalisation * * Report as SAE	1 = Resolved 2 = Resolving 3 = Not Resolved 4 = Resolved with sequelae 5 = Fatal 6 = Unknown	1 = Yes 2 = No

Example of Recording Reactogenicity

Example of recording reactogenicity:

Participant ID |___|___|___|___|___| Participant's Initials |___|___|___| Sex |___| (m/f)

FIELD WORKER VISIT CARD (TO BE COMPLETED ONLY BY FIELD WORKER)

	DAY 1 Enter Date ____/____/____ Enter time ____:____			DAY 2 Enter Date ____/____/____ Enter time ____:____		
ADVERSE EVENT SINCE LAST VISIT	PRESENT	Describe intensity* /diameter, and action taken	Any other comments	PRESENT	Describe intensity* /diameter, and action taken	Any other comments
Pain at injection site	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Limitation of leg movement	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Redness/discoloration at injection site	No ☐ Yes ☐	Diameter |__|__| mm		No ☐ Yes ☐	Diameter |__|__| mm	
Swelling at injection site	No ☐ Yes ☐	Diameter |__|__| mm		No ☐ Yes ☐	Diameter |__|__| mm	
Vomiting	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Diarrhoea	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Excessive crying	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Refusal to feed	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Fever reported by carer	No ☐ Yes ☐	Grade |__| Action |__|		No ☐ Yes ☐	Grade |__| Action |__|	
Other adverse event		Grade |__| Action |__|			Grade |__| Action |__|	
Vital signs	Temp |__|.|__| °C Pulse |__|__|__| Beats/min Resp. Rate|__|__| /min			Temp |__|.|__| °C Pulse |__|__|__| Beats/min Resp. Rate|__|__| /min		
If not seen, reason:						
Any other comments:						
Field worker name:						

If necessary, the participant will continue to be seen regularly after the third day until the symptom(s) have resolved

*Intensity Grade (localised pain and/or limitation of leg movement	*Intensity Grade (all other events)	Action
1 = Painful on touch, no restriction in movement of limb 2 = Painful when limb is moved 3 = Unable to use limb due to pain	1 = Present but easily tolerated 2 = Interferes with daily activities 3 = Prevents daily activities	0 = No action taken 1 = Medication 2 = Non-Drug therapy 3 = Hospitalisation

Key Points to Remember

- The collection of AEs is a regulatory requirement and is also clinically and scientifically

important.
- When collecting AEs the most important priorities are that the methods used are systematic and sufficient data are recorded.
- The trial protocol should state what is considered to be an adverse event, how these should be monitored, how it should be recorded, what actions are to be taken, how and when it should be reported, etc.
- The use of clear and precise terms to describe the category of AE is essential.
- An AE is any type of medical event temporally linked to the investigational intervention and may or may not be caused by it.
- An adverse reaction/adverse drug reaction (AR/ADR) is an AE that is, in the opinion of a clinician, causally related to an IMP and could be the occurrence of a disease or condition that directly affects the patient's health, safety or well-being.
- Expected ARs are the 'side effects' that are known about the IMP and have already been documented.
- Unexpected ARs are those that are not consistent with the known, predicted possible effects of the intervention.
- A 'Serious Adverse Event' (SAE) is any AE (which may or may not be related to the intervention) that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
- A 'Serious Adverse Reaction' (SAR) is an SAE where a causal relationship between a medicinal product and the SAE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Key Points to Remember

- A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected SAR that is not expected with this product or intervention.
- Important Medical Events are medical events that may jeopardise the patient, might require intervention to prevent a 'serious' one e.g. allergic bronchospasm, convulsions, etc. and that follow the same requirements as SAEs.
- AEs can be detected through participant interview, observations, measurements or spontaneous reporting.
- AE/SAE follow-up will be dictated by the requirements of the trial.
- The protocol will outline how and when data will be collected on AEs.
- AEs are usually graded according to intensity.
- Severity refers to the intensity of the AE e.g. Grade 2 = moderate, whereas seriousness refers to the outcome e.g. life threatening.
- Systemic AE, whether expected or not and whether serious or not, needs to be assessed for causal relationship. The assessment should be based on the time of occurrence, medical history, other medication or procedures, erroneous administration of product and other factors.
- SAEs (which include SARs and SUSARs) should be reported to the coordinator or principle investigator and to the sponsor immediately (within 24 hours) of becoming aware of the event.
- There are two recognised justifications for unblinding when treatment of the effected participant relies on it and when the sponsor requires the information to report an SAE to the regulatory authorities and ethics committee. In addition, occurrence of pregnancy might require unblinding.
- AEs are monitored in clinical trials to determine whether there are any significant concerns that would prevent the IMP from being used in its target population.

References, Resources and Tools

References

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2. Friedman LM, Furberg CD, Demets DL. Fundamentals of Clinical Trials 4th Ed. 2010, Springer, New York.
3. Hackshaw A. A Concise Guide to Clinical Trials 2009, Wiley-Blackwell, Chichester.
4. Liu MB and Davis K. A Clinical Trials Manual from the Duke Clinical Research Institute: Lessons from a Horse Named Jim 2nd Ed. 2010. Wiley & Sons, Chichester.
5. Loke Y K and Derry S. Reporting of adverse drug reactions in randomised controlled trials – a systematic survey: BMC Clinical Pharmacology 2001; 1: 3.
6. Mulay M. A Step-by-Steve Guide to Clinical Trials 2001, Jones & Bartlett, London.
7. NIMH Multisite HIV Prevention Trial Definition of adverse reactions in clinical trials of a behavioural intervention: AIDS 1997 11(P): S55-S57.

Resources

- Consort Statement (revised) 2010
- Consort Statement 2010; explanation and elaboration
- FDA Toxicity Grading Scale 2007
- Global Health Trials Glossary 2011
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1) 1996
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Harmonised Tripartite Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, E2A 1994
- Division of Acquired Immunodeficiency Syndrome (DAIDS) adverse events grading scale

Tools

- Sample MRC Adverse Events Form
- Sample MRC Reactogenicity Form
- Examples of consent form templates

Quiz

Summary

1. The guidelines by international organisations such as the WHO, ICH and CIOMS advice that AEs are:
    - Only recorded in the case of serious injury or death
    - Carefully and systematically recorded
    - A routine part of all studies and should be ignored
2. The study protocol should provide which of the following:
    - A list of what is considered to be an adverse event
    - What actions are to be taken
    - Details of how these should be monitored
    - Details of how they should be recorded
    - How they should be reported
    - When they should be reported
    - All of the above
    - None of the above
3. Consistent and precise definitions of what constitutes an AE are important because:
    - Ambiguous data collection makes analysis difficult

- Auditors expect consistent record keeping
- RECs require the use of preferred terms in the study documentation

4. ARs/ADRs are always expected:
   - True
   - False
5. Reporting of SAEs is up to the discretion of the investigator:
   - True
   - False
6. A SAR is one that can be:
   - A mild rash easily treated with topical cream
   - A reaction requiring hospitalisation
   - An event that does not need to be recorded
   - An event that will always cause the trial to be stopped
7. Which of the following is a method used to detect AEs:
   - Observations
   - Measurements
   - Interviewing the patient
   - Spontaneous reporting
   - All of the above
   - None of the above
8. The methods used for collecting and recording AE data are outlined by:
   - The protocol
   - The Research Ethics Committee
   - The Data Safety Monitoring Board
   - The statistical analysis plan
9. Which of the following is not used as an AE assessment of a causal relationship?
   - Participant’s medical history
   - Participant’s physical fitness
   - Erroneous administration of product
   - Other factors
10. SAEs are not normally reported to which of the following groups:
    - Sponsor
    - Funder
    - Safety Monitor/ Data Safety Monitoring Board
    - Ethics Committee
    - Trial Steering Committee
    - Others (e.g. Manufacturer, Collaborators, etc.)
11. A study with adult participants is never unblinded:
    - True
    - False
12. Which of the following statements is correct?
    - Unblinding is justified when a participant has experienced an AE and requires treatment which cannot be given without knowing the study arm
    - Unblinding is justified when the sponsor requiring the unblinding information to report a SUSAR to the regulatory authorities and ethics committee.
    - Both above are true
    - Neither is true

Submit