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Guidance Document:

Lab Management for Determining and Reporting Adverse Events

Overview

This guidance will help you establish a lab protocol for identifying and reporting Adverse Events.

Definitions

DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). All adverse events after the time of informed consent will be recorded.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Suspected adverse drug reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered **"serious"** if, in the view of either the Site Principal Investigator/Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect in a biologic child (if within 1 year of the study)
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Classification of Adverse Events

SEVERITY OF EVENT

A study team member will be responsible for determining the severity of each AE.

Common Toxicity Criteria for Adverse Events (CTCAE) (latest version available at time of study start – currently version 5.0) will be used to assess and grade adverse event severity, including laboratory

abnormalities judged to be clinically significant. If the event is not covered in the CTCAE, the guidelines shown in the following table will be used to grade severity.

For adverse events (AEs), the following guidelines will be used to describe severity:

- Mild (Grade 1) – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate (Grade 2) – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe (Grade 3) – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- Life Threatening (Grade 4) – The participant is at risk of death due to the adverse event as it occurred. This does not refer to an event that, hypothetically, might have caused death if it were more severe.
- Death (Grade 5) – Death related to adverse event

RELATIONSHIP TO STUDY INTERVENTION

A study team member who is a Licensed Provider will be responsible for determining the relationship of each AE to the study intervention.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", or downgraded to …, as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the Licensed Provider.

EXPECTEDNESS

A study team member who is a Licensed Provider will be responsible for determining whether an AE is expected or unexpected.

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the FDA label and protocol.

Time Period and Frequency for Event Assessment and Follow-Up

A properly delegated study team member will record all adverse events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study drug administration. All events will be followed for outcome information until resolution or stabilization.

All AEs occurring while on study will be documented regardless of their relationship to the study intervention, and whether or not they meet the definition of an SAE. AEs will be captured, reviewed and assessed by an LIP member of the study team. The outcome of this review and assessment will be documented by a properly delegated study team member on an Adverse Event Log. Information to be collected includes event description, time of onset (start date) and time of resolution/stabilization of the event (end date), and the LIP's assessment of expectedness, severity and relationship to study intervention.

Any medical condition that is present at the time the participant is screened will be considered as baseline medical history and will not be recorded as an AE. However, if the study participant's condition deteriorates at any time during the study, the event will be recorded as an AE.

Changes in the severity or frequency of an AE will be documented separately to allow an assessment of the duration of the event at each level of severity or frequency.

AEs characterized as intermittent will be documented with onset and duration of each episode.

At each study visit, a properly delegated study team member will document all occurrences of AEs and SAEs since the last visit. This information will be gathered through direct observation (e.g. rash), elicited from or spontaneously volunteered by the participant, documentation in medical records, laboratory or other clinical reports or notes, or identified in patient-reported outcome tools (e.g. surveys, questionnaires), or any other means.

Adverse Event Reporting

Adverse Event Reporting will be performed in accordance with the study protocol, any contractual agreement, and all IRB requirements.

Reporting to US Food and Drug Administration (FDA)

SAEs that do not meet the criteria for prompt reporting will be included as a summary report to the FDA. A narrative or tabular summary showing the most frequent and most serious adverse events by

body system will be provided by the Sponsor to the FDA with each annual report in compliance with 21 CFR 312.33(b)(1)

Adverse Device Effects

Adverse Device Effects (ADE) is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

Serious ADE is an ADE that has resulted in any of the consequences characteristic of a serious adverse event (SAE) that led to:

1. death
2. fetal distress, fetal death or a congenital abnormality or birth defect or
3. a serious deterioration in health that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or required in-patient hospitalization or prolongation of existing hospitalization, or resulted medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

Classification of an Adverse Device Effect

EVENT SEVERITY

The investigator will classify ADE severity according to the following scale:

- Mild: Minor discomfort noticed but does not interfere with normal daily activity
- Moderate: Discomfort reducing or affecting normal daily activity
- Severe: Incapacitating with inability to work or perform normal daily activity

RELATIONSHIP TO STUDY INTERVENTION

The investigator will assess the relationship of ADEs to study intervention using the categories below:

- Related: The AE is known to occur with the study intervention or there is evidence to suggest a causal relationship between the study intervention and the AE.
- Potentially Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- Not Related: There is no evidence to suggest a causal relationship with study intervention or an alternate etiology has been established.

ANTICIPATION

Unanticipated ADE: any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with the study device, if that effect, problem, or death was not

previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with the application that relates to the rights, safety, or welfare of participants.

All serious adverse device effects (SADEs) will be collected from the time of informed consent until 30 days after the last use of the device. All SADEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable. Follow up may be conducted by medical record review or communication with the participant's health care provider.

Adverse Device Effect Reporting

The investigator will report of ADEs to the regulatory authorities per requirements. The investigator will also report suspected unanticipated SADEs to the IRB, per IRB reporting guidelines.

Questions?

If you have any question about this guidance, please contact the IRB at irbadmin@colorado.edu