

# THE IMPACT AND RESPONSIBILITIES

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*of the*

## Clinical Research Associate (CRA)

*on the Accuracy of*

## Adverse Event Reporting

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The Clinical Research Associate (CRA) is the primary representative of the sponsor and arguably has the most direct impact on the proper and accurate reporting of adverse events in clinical trials. This impact is encompassed within the following responsibilities:

- The CRA is often the first sponsor representative to meet with and visit the investigator during a pre-study site visit.
- The CRA is involved in the initial training and communication of adverse event reporting requirements with the investigator, by filling either a primary or support role in the study initiation visit meeting or multi-center investigator meeting.
- The CRA is the first line of communication between the sponsor and investigator throughout the study.

One of the most critical functions of the CRA is to assure that investigators are fully aware of, and comply with, their responsibilities for adverse event reporting. To achieve this, the CRA must often teach the adverse event reporting requirements to investigators. Consequently, the CRA must be knowledgeable about both the regulatory and sponsor-specific requirements for reporting serious and non-serious adverse events in clinical trials. This includes the proper use and completion of the sponsor's data collection forms, as well as definitions and terms of reporting adverse events that may extend beyond the regulatory requirements.

There are five major areas of responsibility through which the CRA can impart knowledge of adverse event reporting to investigators:

- Providing initial training on adverse event reporting requirements for investigators;
- Reviewing data to assure accuracy and completeness of reported events;
- Providing new information to the investigator;
- Monitoring the clinical trial to detect potentially unreported adverse events; and
- Assuring follow-up data is reported for adverse events when required.

Let us review these responsibilities in more detail.

### **CRA Action 1 Providing Initial Training on Adverse Event Reporting Requirements**

The initial training on adverse event reporting requirements should begin at the pre-study site visit meeting by assessing the investigator's understanding of GCP requirements.

The investigator should be minimally trained in the regulatory basis of adverse event reporting including:

**Definitions** (Terms extracted from the ICH GCP Guideline or FDA 21 CFR 312.32):

**Adverse Drug Reaction (ADR)**

*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.*

*Regarding marketed medicinal products, a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (ICH GCP Guideline).*

**Adverse Event (AE)**

*An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH GCP Guideline).*

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**

*Any untoward medical occurrence that at any dose:*

- Results in death;*
- Is life-threatening;*
- Requires inpatient hospitalization or prolongation of existing hospitalization;*
- Results in persistent or significant disability/incapacity; or*
- Is a congenital anomaly/birth defect (ICH GCP Guideline).*

Some sponsors add additional criteria to this ICH/FDA required list, such as “any event the investigator considers to be a medically serious event.” FDA’s 21 CFR 312.32 regulation states: “Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may

*jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”*

*Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug (21 CFR 312.32).*

*Disability: A substantial disruption of a person's ability to conduct normal life functions (21 CFR 312.32).*

*Life-threatening adverse drug experience: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death (21 CFR 312.32).*

*Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended (21 CFR 312.32).*

The CRA must understand and effectively communicate the use and meaning of these terms in the clinical study setting and adverse event reporting process.

## Investigator Reporting Requirements

FDA regulations require the following from investigators:

*Investigator reports:*

*(a) Progress reports. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under Sec. 312.33 to submit annual reports to FDA on the progress of the clinical investigations.*

*(b) Safety reports. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse*

effect is alarming, the investigator shall report the adverse effect immediately.

(c) *Final report.* An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation (21 CFR 312.64).

Additional requirements are found on FDA 1572 Form "Statement of Investigator."

### Sponsor Requirements

FDA also regulates sponsors with respect to adverse event reporting, particularly regarding the time requirements for reporting serious adverse events to both FDA and investigators, as described in these FDA requirements:

*"Sponsors are responsible for ... providing them (investigators) with the information they need to conduct an investigation properly (21 CFR 312.50)."*

*Written reports.* The sponsor shall notify FDA and all participating investigators in a written IND safety report of:

(a) Any adverse experience associated with the use of the drug that is both serious and unexpected; or

(b) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32).

*Telephone and facsimile transmission safety reports.* The sponsor also shall notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than seven calendar days after the sponsor's initial receipt of the information (21 CFR 312.32).

*Review of ongoing investigations.*

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under Sec. 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with Sec. 312.33 (21 CFR 312.56).

## Applying the Regulatory Requirements to the Process of AE Reporting

Teaching investigators about adverse event reporting should always be done in a professional, cooperative and collaborative manner. The model described in **Figure 1** may be useful in helping to explain the adverse event reporting requirements to investigators.

### Two critical issues for investigators to understand are:

- Clinical research does not equal daily medical practice; and
- All events occurring in a clinical study subject are reported, without regard to the investigators opinion of relationship of the event to the test drug.

## CRA Action 2 Reviewing Data to Assure Accuracy and Completeness of Reported Events

A primary job responsibility of the CRA is monitoring clinical study documents. This monitoring may occur during a site visit or off-site for documents that are sent directly to the CRA.

This requires intimate familiarity with the sponsor's adverse event reporting forms, which may differ for serious adverse events and non-serious adverse events. Each sponsor's reporting forms may differ in format and appearance, but the information required usually remains the same.

The CRA should begin by reviewing the adverse event report. Each field should be evaluated for the presence of accurate, medically or clinically logical information. For example, accuracy may be determined by verification of the information in a medical record or other source document. There must be no discrepancy between the source records and the adverse event report.

Assessment of medical or clinical logic requires the CRA to be knowledgeable of pathology and normal physiology, as well as pharmacology and toxicology of the drug under study. Adverse events reported as observed in

**Figure 1**

**A Model for Explaining AE Reporting Requirements to Investigators**

Questions the Investigator Must Ask	Actions the Investigator Must Take
<p>1. Has an event occurred that is not of benefit to the subject?</p>	<p>If YES, move to question 2 to determine the time requirement for reporting the event to the sponsor.</p> <p>If NO, no event is reportable.</p>
<p>2. Is the event serious, according to the clinical study definition of serious?                      “Any untoward medical occurrence that at any dose:</p> <ul style="list-style-type: none"> <li>• Results in death;</li> <li>• Is life-threatening;</li> <li>• Requires inpatient hospitalization or prolongs existing hospitalization;</li> <li>• Results in persistent or significant disability/incapacity; or</li> <li>• Is a congenital anomaly/birth defect.”</li> <li>• Any additional sponsor-defined requirement, as stated earlier.</li> </ul>	<p>If YES, report the event to the sponsor in accordance with the required time frame. Most sponsors require the event to be immediately reported, but no longer than 24 hours after the investigator becomes aware of it.</p> <p>If NO, report the event in compliance with the sponsor’s requirements for non-serious events.</p>

pre-clinical studies provide an indicator of body systems or events that may be observed in human subjects. Therefore, the CRA should have a thorough understanding of all clinically related information in the Investigator Brochure. The best way to obtain this understanding is for the CRA to comprehensively review the Investigator

Brochure and obtain answers to any questions or area clarification about information that is not fully understood.

Medical or clinical logic also is evaluated by employing knowledge of disease conditions and appropriate treatments of those conditions. For example, if an adverse event of a sprained ankle is reported in an allergy study, it would be medically logical to see treatment of the adverse event with analgesic or anti-inflammatory compounds, such as aspirin or ibuprofen. On the other hand, it would not be as logical to see an antibiotic or antihypertensive drug prescribed for a sprained ankle. If an apparent inconsistency between the reported event or disease condition and treatment reported for the event exists, the CRA should discuss the reported information with the investigator to assure the reported information is completely accurate.

**CRA Action 3  
 Providing New  
 Information to  
 the Investigator**

The CRA is partially responsible for assuring compliance with the sponsor’s responsibility to provide any new information to the investigator during the course of the study, as defined in the IND regulations as follows:

*Informing investigators:*

*(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with Sec. 312.32 (21 CFR 312.55).*

Informing investigators of new information may be done by providing:

- (1) A revised package insert;
- (2) Newly reported adverse events;
- (3) Updated adverse event incidence data;
- (4) New clinical trial efficacy results.

It is important for the CRA to note that any event that would trigger a notification to investigators, also may require an update to the informed consent document for active studies.

## **CRA Action 4 Monitoring to Detect Potentially Unreported Events**

The CRA should be continually monitoring the study during on-site visits to review records, as well as through telephone, fax or email communications in the interim. Specific items the CRA should check, which may be indicative of an unreported adverse event, include:

- Addition of concomitant medications at any visit;
- Assessment of symptoms reported by the subject;
- Subject diaries; and
- All medical record entries occurring after the initial study visit date and prior to the study end date.

## **CRA Action 5 Assuring Follow-up Information is Reported for Adverse Events, When Required**

The CRA should evaluate all reported adverse events to assess the need for obtaining a follow-up report from the investigator. Examples of clinical situations that might require a follow-up report include:

- (1) A serious adverse event for which complete information was not available for the initial report;
- (2) A previously reported adverse event, for which any new or changed information becomes available;
- (3) Resolution of a previously reported unresolved adverse event;
- (4) Early termination by a subject for whom an unresolved event was reported; and
- (5) Study completion by a subject for whom an unresolved event was reported.

## **Conclusion**

The CRA has significant impact upon the complete and accurate reporting of adverse events by investigators in clinical trials.

The CRA must pay careful attention to the details of adverse event reporting throughout communications with investigators. The CRA should use monitoring to ensure compliance with the adverse event reporting requirements and assure follow-up reporting when appropriate.

Careful attention to the details of adverse event reporting by the CRA will, without doubt, help to assure the complete and accurate reporting of adverse events in clinical trials.

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