From: OC GCP Questions
To: [redacted]
Subject: Adverse Event review
Date: Friday, September 12, 2014 12:56:14 PM

Good afternoon:

The situation that you describe below appears to not conform with good clinical practice policies. It is the investigator's responsibility to report serious adverse events to the sponsor. Please see the detailed information below. Pre-signing and pre-filling out CRFs does not conform with good clinical practice policies either.

The investigator is required to report serious adverse events to the sponsor and must include an assessment of whether there is a reasonable possibility that the drug caused the event (21 CFR 312.64). The sponsor is required to report serious and unexpected suspected adverse reactions to FDA and all participating investigators (21 CFR 312.32(c)(1).

The investigator should follow the protocol regarding the format for reporting the investigator's causality assessment to the sponsor. The IND safety reporting draft guidance includes the following:

"The sponsor should decide how to capture the investigator's causality assessment (e.g., rating scale, yes/no response to a question such as, "Was there a reasonable possibility that the drug caused the adverse event?")."

Additionally "causality" is mentioned throughout the document below.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

As stated above, the investigator should report adverse events to the sponsor in accordance with the protocol, ensuring that at a minimum the investigator is complying with 21 CFR 312.64(b) (e.g., immediately report serious adverse events to the sponsor, report non-serious adverse events in accordance with the protocol): http://edocket.access.gpo.gov/cfr_2004/aprqtr/21cfr312.64.htm .

Please find the ND safety reporting final rule and draft guidance at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm

In response to your questions below, the assessment of causality that determines whether an event represents a suspected adverse reaction is the sponsor's responsibility. The sponsor should take the investigator's view into account when determining if an event qualifies for reporting. However, sponsors should not report events for which the sponsor assesses there is no causal relationship between the drug and the event, regardless of the **investigator's assessment of causality.**

Investigators are required to promptly report "to the IRB all unanticipated problems involving risk to human subjects or others," (21 CFR 312.66). The term unanticipated problem used in the Adverse Event Reporting to IRBs guidance describes adverse events and other types of problems (i.e., adverse events are a subset of unanticipated problems) that investigators are required to report to RBs. The final rule on ND safety reporting does not directly address safety reporting by investigators to RBs.

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, information about adverse events must be communicated among investigators, sponsors, and IRBs (ethics committee) as follows:

Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report "as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information" of "any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)). And, more generally, sponsors are required to "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" (§ 312.55(b)).

Prior to initiation of a study at a site, information must be provided to the IRB (EC) for review. The IRB needs information on risks to subjects in order to allow the IRB to assure that these risks are reasonable in relation to the anticipated benefits (21 CFR § 56.111(a)(2). Such information would include adverse events that have occurred with the use of the drug. As noted above, once the study is approved, investigators are responsible for reporting to the IRB unanticipated problems, which may include adverse events.

As you are probably aware, it is often several years after the close of a clinical study before a sponsor submits the results in support of a marketing application to FDA. In addition, there have been times when seemingly unrelated SAEs have been revealed as related to use of the drug when information across multiple sites is compiled, thus including larger numbers that can make rare events apparent.

Kind regards,

Doreen M. Kezer, MSN
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Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [redacted]
Sent: Friday, September 12, 2014 10:23 AM
To: OC GCP Questions
Subject: Adverse Event review

To Whom t May Concern:

I am monitoring an IDE study and, during an initial monitor visit, observed that a study coordinator who is not medically degreed has been completing the adverse event (AE) source documentation including the assessment of causality and providing this documentation to the investigator for his signature; there is no signature by her attributing her entries on this form so, it appears that the form was solely completed by the Investigator. During my visit, I found numerous AE source worksheets that had been "pre-filled" by the study coordinator that were unsigned; I also found several AE source worksheets that were pre-signed by the Investigator without the causality assessment(s) and other info completed. The protocol does state that the Investigator is to determine all adverse events, report them , and complete the adverse event case report form. The Delegation Log being used is not very specific and only has a choice for "observe adverse events."

Given the information and scenario above, under what circumstances would the FDA find it acceptable for a non-medically degreed study coordinator to be determining the causality for adverse events in a clinical research study? The case where a source form has been pre-signed by the investigator and to be filled in later by the study coordinator is obviously not GCP standard?