From: OC GCP Questions
To: [redacted]
Subject: Signature Question
Date: Monday, September 22, 2014 2:08:15 PM

Good afternoon:

t is the investigator's responsibility to report serious adverse events to the sponsor and the IRB. You also indicate that your protocol states that the AEs will be evaluate by a physician.

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 The IND safety reporting draft guidance includes the following: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Please find the ND safety reporting final rule and draft guidance at: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: Monday, September 22, 2014 9:33 AM
To: OC GCP Questions
Subject: RE: Signature Question

Hi This is [redacted] and I have a question regarding Obtaining and Evaluating AEs

We have a trial where a certified RN is obtaining AEs and evaluating common minor AEs (Headache) and something that could potentially be more severe

In our protocol we have defined AEs of **special interest** which includes those more severe AEs expected as part of the treatment (e.g. hyperresponse) and these are required to be evaluated by a physician. Is a trained nurse able to differentiate between common minor AEs (Headache) and something that could potentially be more severe?

In addition, for both cases the RN is listed on the **Delegation of Authority Log** as being authorized by the PI to perform these tasks

Is this acceptable??
[redacted]