From: OC GCP Questions
To: [redacted]
Subject: FDA"s position on 21 CFR 312.32 IND safety reporting - Expected/Unexpected adverse event
Date: Tuesday, August 12, 2014 9:36:08 AM

Good morning –

Based on the limited information in your email, I would say that the hospitalization would be considered an unexpected event.

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 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.

312.32(c)(1)(iv) requires sponsors to report in an IND safety report a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (i.e., these are expected events). Unexpected and serious as well as when to report a SAE is explained in the guidance in detail below. If the study is under ND, you can always consult the FDA review division that is overseeing your study for more specific guidance.

FDA has a guidance document titled, "Guidance for Clinical Investigators, Sponsors, and RBs Adverse Event Reporting to IRBs - Improving Human Subject Protection" that can be found at http //www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079753 pdf. The guidance document provides recommendations for sponsors and investigators conducting IND trials to help them differentiate between those adverse events that are unanticipated problems that must be reported to an RB and those that are not. It also outlines what is considered a serious unexpected AE.

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

I hope this information is helpful. Please contact us again at gcp questions@fda hhs.gov should you have additional questions.

Kind regards,

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Office of Good Clinical Practice
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From: [redacted]
Sent: Monday, August 11, 2014 2:26 PM
To: OC GCP Questions
Subject: FDA's position on 21 CFR 312.32 IND safety reporting - Expected/Unexpected adverse event

Hi,

The way I interpret the categorization of expectedness of an adverse event is basing on its severity as noted in the protocol or the Investigator's brochure. What if dizziness is noted as an expected event in the protocol and subject was hospitalized and treated for dizziness. Does the hospitalization be considered as unexpected event, since the event was not noted on such a severity in the protocol or Investigator's brochure?

Does the protocol or investigator's brochure need be specific about severity of all expected adverse events or a mere mention of the event is enough to consider it an expected event.

Thanks in advance for your guidance.

Regards,
[redacted]