From: OC GCP Questions
To: [redacted]
Subject: Question regarding SAE reporting
Date: Thursday, October 30, 2014 1:11:45 PM

Good afternoon --

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. The guidance also makes suggestions about how to make communicating adverse events information to IRBs more efficient. As stated in section II, page 2:

For clinical investigations of drug and biological products conducted under an IND application, information about adverse events must be communicated among investigators, sponsors, and IRBs as follows:
Investigators are required to report promptly "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" (§ 312.64(b)).

Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report 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)).

Investigators are required to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).
A critical question for studies conducted under part 312 is what adverse events should be considered unanticipated problems that merit reporting to an RB.

The protocol can specify the type and severity of AEs that require reporting to the sponsor with any urgency. That said if you plan to evaluate the frequency of repeat hospitalizations, then the protocol can be written that the hospitalizations are not considered AEs. Please remember the IRB would need to approve the protocol.

A discussion related to this issue occurs in FDA's draft guidance "Safety Reporting Requirements for NDs and BA/BE Studies" (available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf). This draft guidance was issued in concert with FDA's final rule, which published on September 29, 2010, "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products." Information on this final rule is available at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358 htm

If you have additional specific questions related to AE reporting, you may contact CDER, Office of Medical Policy directly. CDEROMP@fda hhs.gov

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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From: [redacted]
Sent: Thursday, October 30, 2014 1:05 AM
To: OC GCP Questions
Subject: Question regarding SAE reporting

In a prior contact, you clarified that worsening of the outcome of interest should not be identified as an adverse event (e g , worsening of back pain in a trial of a back-pain treatment should not be designated as an AE as failure of therapy is an expected outcome of treatment) My question now is whether this also applies to serious adverse events Here are the specifics: we are planning to conduct a randomized clinical trial of a home visit by a medical resident for patients with a history of frequent prior hospitalizations The outcome of this trial is the frequency of repeat hospitalizations in the 6 months following the index hospitalization My question is whether overnight hospitalizations, that under other circumstances would generally be reported as SAEs, should not be so reported because they are the outcome of interest and it is expected that many of the participants in this trial will experience further hospitalizations following discharge from the index hospitalization Thanks very much for your guidance

[redacted]