From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Tuesday, September 06, 2005 11:10 AM
To: [Redacted]
Subject: RE: Questions arising from an audit

Dear [Redacted]:

In answer to the first question: The third questionnaire should also have been provided to the IRB. 21 CFR 56.109(a) states, "An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations." Because the third questionnaire was "completed at the Baseline Visit during an interview with the subject," it is would seem to be encompassed as a research activity requiring IRB review and approval. I'm somewhat surprised that the IRBs did not require that the site produce the third questionnaire before approving the research.

In answer to the second question, the short answer is that the changes should have been promptly reported to the IRB, and that any changes should not have been made without prior IRB review and approval, unless the change was necessary to eliminate apparent immediate hazards to human subjects. If the changes were indeed minor, it may have been possible for the IRB to review the changes under the IRB's expedited review procedures.

Here is the long-winded version:

There is only one instance in the regulations, that I'm aware of, where the word "deviation" appears, and there are several references to protocol "deviations" in ICH E6, Good Clinical Practice: Consolidated Guidance:

- 21 CFR 312.23(a)(6)(ii) states, "A protocol for a Phase 2 or 3 investigation should be designed in such a way that if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy."
- The ICH E6 guidance does not define the term "protocol deviations"; the references containing the term are in the context of planned or unplanned departures from a study protocol.

That said, FDA's regulations have numerous references to "changes" or "amendments" to study protocols. For example, 21 CFR 312.30 addresses the responsibility of sponsors to submit amendments to their IND(s) to ensure that clinical investigations are conducted according to protocols included in the application. 21 CFR 312.30(b) specifically discusses changes in a protocol, and

provides several examples of changes that would require sponsors to submit protocol amendments to the IND.

Clinical investigators have specific responsibilities with respect to "changes" in a protocol. For example, when a clinical investigator signs the 1572, he/she indicates a commitment to "conduct the study(ies) in accordance with the relevant, current protocol(s)" and promises that he/she "will only make ***changes*** in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects". [21 CFR 312.53(c)(1)(vi)(a).] Clinical investigators are also required to promptly report to the IRB, all "***changes*** in the research activity"..." and, further, ***are prohibited from "mak[ing] any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects."*** [See 21 CFR 312.66] (Emphasis added.)

The regulations and ICH E6 are posted on FDA's GCP website (http://www.fda.gov/oc/gcp). You could search the regulations on the key words "changes", "amendment", and "modification" if you wanted to compare all of the references.

I hope this is helpful.

Sincerely,

Carolyn Hommel
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This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

-----Original Message-----
From: [Redacted]
Sent: Monday, September 05, 2005 5:37 PM
To: OC GCP Questions
Subject: Questions arising from an audit

Dear colleagues (David, Stan, Patricia, Bonnie, Carolyn, et. al.),

I want to take this opportunity to again thank you for providing me with help to questions sent to me by monitors, study coordinators, physicians and auditors. Your opinions and answers to GCP questions are very much appreciated.

Here are two more questions for you to ponder:

1. A protocol describes the use of three (3) different questionnaires in a study. The protocol appendices only included two out of the three questionnaires. The protocol with two of the three questionnaires was submitted to the IRB (Central IRB and/or local IRB). None of the IRBs received the third questionnaire for review and approval. The Sponsor said that the third questionnaire was only used as a "tool" to select subjects for the study. However, the third questionnaire was completed at the Baseline Visit during an interview with the subject. An audit observation was made with respect to this "third" questionnaire stating that in the opinion of the auditor, the third questionnaire should have been included as an appendix in the Protocol (as the other two questionnaires had been done previously). The audit observation also notes that the third questionnaire should have been submitted to the IRB for approval. The Sponsor disagrees. What is your opinion and is there a regulation or guideline that you might cite?

2. The sponsor has granted many waivers for protocol inclusion. The waivers consisted of granting approvals for patients to enter the study who did not meet all inclusion criteria. For example, the subject's age did not meet the range described in the protocol; a qualifying medical test was done outside the timelines described in the inclusion criteria, etc. Audit recommendations were that the Sponsor should provide the IRBs (Central IRB and/or local IRBs) with the Waivers granted by the Sponsor for inclusion criteria. The Sponsor indicated that these were minor deviations from the protocol, and that they did not have to be provided to the IRBs for their information. What is your opinion and is there a regulation or guideline that you might cite?

Again, thank you for your help.

Kind regards,
[Redacted]