From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Wednesday, June 07, 2006 2:58 PM
To: [Redacted]
Subject: RE: DrugInfo Comment Form FDA/CDER Site

Dear [Redacted]:

The term "significant deviations" is not defined in FDA's regulations; however, my office is sometimes asked what is the difference between a "protocol deviation" and "protocol violation".

In fact, I could find only one instance in FDA's regulations where the word "deviation" appears. Title 21 of the Code of Federal Regulations, Part 312.23(a)(6)(ii) [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."

There are several references to protocol "deviations" in sections of the ICH E6 Good Clinical Practice Consolidated Guidance [http://www.fda.gov/cder/guidance/959fnl.pdf], in the context of planned or unplanned departures from a study protocol, but the E6 guidance does not define the term. You may find the above guidance useful in understanding FDA expectations relating to protocol deviations, and you may wish to search the guidance on the key word "deviation" to identify all of the references to this topic.

The term "protocol violation" does not appear anywhere in FDA's regulations nor does it appear in the ICH E6 guidance.

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 also 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". [See 21 CFR 312.53(c)(1)(vi)(a).] The clinical investigator is also required to promptly report to the IRB all "changes in the research activity"..." and, further, is prohibited from "mak[ing] ANY changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects." [Emphasis added; see 21 CFR 312.66] You may wish to search the regulations on the key words "changes", "amendment", and "modification" to identify additional references to this topic.

I hope this is helpful.

Sincerely,

Carolyn Hommel
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Good Clinical Practice Program
Office of Science and Health Coordination
Office of the Commissioner
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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: Tuesday, May 30, 2006 2:30 PM
To: CDER DRUG INFO
Subject: DrugInfo Comment Form FDA/CDER Site

Name: [Redacted]

E-Mail: [Redacted]

Comments: Does the FDA provide any guidance on "significant deviations" for human clinical trials? What might the FDA define as a significant deviation? What related/relevant information might be collected? Is there a suggested template form for the report?

Any guidance that is available is welcome.

Thank you!

[Redacted]