From: Toth-Allen, Jean
Sent: Tuesday, April 04, 2006 1:13 PM
To: [Redacted]
Subject: RE: Protocol deviations

Dear [Redacted]:

Thank you for your inquiry regarding protocol deviations/violations.

As you probably have seen, neither the regulations governing studies with investigational pharmaceuticals (21 CFR part 312) nor those for investigational devices (21 CFR part 812) define either a deviation or a violation from the protocol. Regulations speak instead about the requirement for complying with the investigational plan, which includes the protocol, and the responsibility of the sponsor to ensure the compliance of clinical investigators. The ICH GCP guidance, found at http://www.fda.gov/cder/guidance/959fnl.pdf, talks about compliance with the protocol (4.5) and discusses deviations. From FDA's perspective, deviations and violations are synonymous terms - they mean the protocol, as written, was not strictly adhered to. There are, however, some distinct differences among what can be considered as protocol deviations.

There is a deviation from the original protocol with which the sponsor has agreed and an appropriate protocol amendment has been approved by the IRB. Such would not be considered a deviation during an FDA inspection but rather a sanctioned change, unless it was implemented prior to IRB approval. A sponsor may also allow an individual who does not meet the inclusion/exclusion criteria to enter the study under certain conditions. While not in the best interests of the integrity of the study data, if an investigator could show the sponsor agreed prior to that subject's initiation into the study, it would not be considered a protocol deviation. (Multiple instances of such exemptions may be considered differently, however.) There are also deviations that occur to protect the safety and/or welfare of the subjects (specifically addressed in regulation at 812.150(a)(4) and 56.108(b)). Such deviations must be reported to the IRB, who may determine a change to the protocol is warranted. However, I am assuming it is this last type you are actually referring to - those deviations that inadvertently or purposely occur without notice or emergency need, e.g., enrolling a subject or subjects who do not meet inclusion/exclusion criteria, without approval by the sponsor, or failing to do a prescribed test or procedure on one or more subjects. Such deviations from the IRB-approved protocol would be considered non-compliance with the protocol and therefore with the applicable regulations, whether you choose to call them a deviation or a violation.

Hope this information is useful.

If you need further information and/or have additional questions, please submit them once again to the official GCP mailbox, gcpquestions@oc.fda.gov, in lieu of responding to my personal e-mail address.

Sincerely yours,
Jean Toth-Allen, Ph.D.
Good Clinical Practices Program
OSHC, Office of the Commissioner, US FDA

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.

From: [Redacted]
Sent: Friday, March 31, 2006 9:00 AM
To: OC GCP Questions
Subject: Protocol deviations

I would like to have a better understanding of a protocol deviation. Our institution does not distinguish between a deviation and a violation and therefore all must be reported. I recently searched your website and remember reading an article giving more insight into this dilemma from the FDA viewpoint. Can you direct me to this particular article.

Thank you for you time,

[Redacted]