From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Friday, May 05, 2006 9:40 AM
To: [Redacted]
Subject: RE: Change in Interpretation to 21CFR 312.30(b)

Dear [Redacted]:

After consulting with other FDA offices, I can provide you with the following information:

As you know, 21 CFR 56.108(a) requires IRBs to follow written procedures "...(3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to human subjects."

In addition, 21 CFR 312.66 states, "...The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity...and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects."

Per 21 CFR 312.53(c)(1)(vi)(a), the investigator also gives his/her commitment to the sponsor, "...to conduct the study(ies) in accordance with the relevant current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects..."

In general, all protocol exceptions must be approved by both the sponsor and the IRB, and appropriately documented, before they are implemented. If a protocol exception has been approved by both the sponsor and the IRB, and appropriately documented, then it generally would not appear on the 483.

Having said that, I would point out that there may be instances in which one or more exceptions may be cited anyway, depending on the number of exceptions involved and the clinical/medical significance of the criterion/criteria for which the exception or exceptions were granted. We also note that numerous ad hoc changes to a study protocol, in effect, would undermine the purpose of IRB review and approval. The IRB needs to be involved, as does the sponsor, prior to making any change, unless it's an emergency situation requiring immediate action.

Furthermore, if numerous exceptions to the protocol are allowed, it may also undermine the study, and, potentially, the usefulness of the data in supporting determinations of safety and/or efficacy. If it appears that such waiver requests from one or more study sites are justified, the sponsor should develop an amendment to the protocol in this regard (see 21 CFR 312.30, generally) so that all sites will function in the same way and the data will be consistent across

sites. If it appears that such waiver requests are seemingly routinely granted, it may be worth exploring with the sponsor to determine if the sponsor has requested a protocol amendment.

Bottom-line, if the change has been approved by the sponsor and IRB, or it's to eliminate immediate hazards, whether it is a single occasion or just a few, it probably will not appear on the 483, though it should still be discussed and included in the establishment inspection report (EIR).

I hope this is helpful.

Sincerely,

Carolyn Hommel
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Good Clinical Practice Program
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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.

From: [Redacted]
Sent: Tuesday, March 21, 2006 6:31 PM
To: [Redacted]
Subject: Change in Interpretation to 21CFR312.30(b)

Dear [Redacted],

Further to my voice-mail, I am following up with a written summary of my question.

It is our understanding that the FDA has recently issued at least two 483's to (a) CRO(s) for what was previously a reasonably common practice in a Phase 1 clinic.

Previous practice in Phase 1 trial would have allowed a relatively minor deviation from a protocol to be documented by prior written approval from the Sponsor of the trial and by the Principal Investigator (PI). An example

is that a note-to-file would be generated and signed by Sponsor and PI if a patient/volunteer weighing 201lb were to be allowed to participate in a trial even if the Exclusion Criteria of the protocol indicated that patients weighing more than 200lb should be excluded.

The regulation governing a protocol change is 21CFR312.30(b):

Changes in a protocol. (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

On the basis of the aforementioned 483's, it seems that the FDA may now be interpreting the word "significantly" differently than before. If one were to take the above example, a protocol amendment would need to be approved prior to allowing a patient weighing 201lb at time of screening into a trial if the patients greater than 200 lb are excluded by the Exclusion Criteria definition. In effect then, all changes of any type would need protocol amendments with the only possible exceptions of administrative changes (e.g. address).

If this is indeed the case, we would appreciate guidance or comment on the matter. We would need to inform our clients that what was previously allowed as an approved and acceptable practice has now changed and that delays or extra work must be incurred in order to remain in compliance.

I thank you in advance for your time and feedback.

Respectfully,

[Redacted]