From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Thursday, October 26, 2006 2:16 PM
To: [Redacted]
Cc: Baxter, Sandra S
Subject: RE: Protocol Waivers

Dear [Redacted]:

Your question was forwarded to me for a response.

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
Consumer Safety Officer
Good Clinical Practice Program
Office of Science and Health Coordination
Office of the Commissioner
U.S. Food and Drug Administration (HF-34)
5600 Fishers Lane, Room 14-B17
Rockville, MD 20857

Phone: 301/827-3340
Fax: 301/827-1169

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: Thursday, September 14, 2006 6:08 PM
To: 'sandra.baxter@fda.hhs.gov'
Subject: Protocol Waivers

Hi Sandra,

Thank you for taking the time to speak with me today. As I mentioned I am a [Redacted] and often times have questions asked of me regarding FDA views.

Often times sites will submit a request for a waiver to have a subject continue in a study even though they either did not meet the inclusion/exclusion criteria or other study criteria and the sponsor will grant the waiver. I have had questions posed to me as to how the FDA would view the granted waivers during a filed inspection.

- Is the site written up on a Form 483 indicating that the waivers are not valid?
- If the sponsor writes conditions for waivers in to the body of a protocol or makes reference that waivers may be granted, would the FDA then find the granting of waivers acceptable?

Thank you.

[Redacted]