From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Tuesday, March 07, 2006 1:55 PM
To: **[Redacted]**

Subject: RE: Questions about drug studies
Dear Ms. **[Redacted]** :

Your e-mail to Stan Woollen in care of the GCP Questions account was forwarded to me for a response, and I must apologize for the delay in responding to you. Stan is no longer in our office -- he has moved over to FDA's Office of Regulatory Affairs, and is handling their Good Laboratory Practices program.

In answer to your first question, if an IND is in effect, the sponsor can proceed with new protocols immediately after submitting them to FDA. It's only the initial IND that requires the 30 day wait. While the review divisions usually provide some type of acknowledgement that a study protocol has been received by FDA, there may not always be a letter to that effect. The IND process is a default system--no word from FDA means the sponsor can proceed with the trial. Having said that, I must point out that there is one exception: for studies conducted under 21 CFR 50.24 (exception from informed consent for emergency research), the sponsor must wait for written acknowledgement from FDA before initiating the study. [See 21 CFR 312. 20(c).]

In answer to your second question, changes in a protocol are required to be submitted to FDA as a protocol amendment. [See 21 CFR 312.30(b).] I have pasted a portion of that regulation into this e-mail for your information and convenience:

(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. Examples of changes requiring an amendment under this paragraph include:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(*a*) The sponsor has submitted the change to FDA for its review; and

(*b*) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

So, the change that you described would have to be submitted to the agency as a protocol amendment. [There is a link to the complete text of the regulations on FDA's Good Clinical Practice website (http://www.fda.gov/oc/gcp).]

In your last scenario, you stated that a sponsor was "... allowing the site ... to monitor itself, with a rationale that "it's only a phase 1 drug study" and that the site could monitor itself since the sponsor did not want to pay for a monitor, as the sponsor felt an outside monitor was not required." FDA's regulations do not differentiate between "phases" of a study in determining whether monitoring is required. Sponsors are required, under 21 CFR 312.50, to "...ensur[e] proper monitoring of the investigation(s)." You may find it helpful to look at the recommendations contained in the following, for additional guidance on assuring proper monitoring of a study:

- ICH E-6, "Good Clinical Practice: Consolidated Guideline," specifically, section 5.18; (link http://www.fda.gov/oc/gcp/guidance.html, then scroll down the list);
- "Dear Gene Therapy IND or Master File Sponsor Letter", specifically item #6; (link: http://www.fda.gov/cber/ltr/gt030600.htm)

In response to your last question, I am not a lawyer, and so cannot really say what your liability would be for "noncompliant activity" in each of the scenarios that you have described. Thus, you might want to have your contract with the sponsor reviewed by a competent attorney who could advise you in this matter.

I hope this is helpful to you, and again, apologize for the delayed response.

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 9C24
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.

-----Original Message-----
From: [Redacted]
Sent: Monday, January 23, 2006 6:54 PM
To: OC GCP Questions
Subject: Questions about drug studies

Dear Stan,

As always, I turn to you for advice on some questions from clients. Currently I serve as a consultant to a company that is implementing a phase 1 drug trial. As part of my firm's "due diligence" my coworker requested a copy of the IND approval letter, which the company could not produce, telling us that the original IND letter is about "20 years old" and that they could legally start any phase 1 trial without requiring FDA written approval of the new phase 1 trial. I disagreed, but they disagreed with me.

A second client stated that if they completed phase 1 of a trial but then sent FDA a submission telling that they were going to increase the drug dosage and continue with a more elaborate phase 1 trial, (including more subjects) that they did NOT need FDA's written approval of that submission before beginning that more elaborate phase 1 trial. I recommended that they file a submission to FDA to get approval and then wait for written acknowledgment to show that FDA received the submission, but the company did not feel that was necessary before going forward with dosing new subjects with a higher dose of study drug. As a monitor, I would like guidance from you on where to look for clarificaiton of whether or not I should be concerned and should include this in my monitoring report.

A third company who requested a bid from us is allowing the site (which I monitored for a previous phase 1 trial) to monitor itself, with a rationale that "it's only a phase 1 drug study" and that the site could monitor itself since the sponsor did not want to pay for a monitor, as the sponsor felt an outside monitor was not required.

I was trained in the device world but have monitored phase 3 trials. I have reviewed 21 CFR part 312 as well as ICH GCP, but I would like direction as to what is required for each phase of a clinical trial, and perhaps, if possible, some guidance as to how to respond to these clients in a way that does not make me, as a consultant, liable for any noncompliant activity. Can you help?

Many thanks, as always.

Kind regards,
[Redacted]