From: Lee, Bonnie on behalf of OC GCP Questions
Sent: Monday, June 12, 2006 11:40 AM
To: [purged]
Subject: RE: FDA GCP Question

Dear [purged],

I apologize for the delay in getting back to you. I found your question a bit strange in part because I couldn't think of a situation which would involve an adverse event (AE)that is unexpected and unusual enough to require an independent review, that would not also rise to the level of a "safety" issue for subjects, possibly requiring among other things, an updated Investigator's Brochure reflecting the unexpected AE. I also am not sure about your role in the research (e.g., a sponsor, CRO, investigator).

If one were to view the AE as an "apparent immediate hazard to subjects", one could probably proceed with the additional review of the scans by the independent site [it's not clear if you're referring to review by a Data Monitoring type Committee or something else] without first obtaining a protocol amendment or IRB review....although both sponsor and IRB would need to be involved after the fact.

It seems to me that even if this is exploratory, if the concern is enough to seek additional review of the AE and CT, it is up to the sponsor to decide what may need to be updated in the protocol and at what point in time. Also, the IRB needs to be involved if a protocol change is proposed in order to evaluate it and determining, among other things, whether the consent form would need to be changed to incorporate the new information.

I think it's difficult to answer your questions in the abstract and believe that to a large extent "it depends" upon the circumstances. You ought to go to the review division for definitive advice on this issue. Some of the variables that I would want to know more about would include: how these scans are described in the protocol; how serious the AE is --the fact that it has occurred "in several studies of the same compound" certainly would make it appear that the increased frequency of the AE was probably related to that compound. Although you say that the additional review is "only exploratory in nature" I would think that if it showed or confirmed some serious problem, it could cause the protocol to be changed to incorporate that additional CT review for all subjects; or some other change or even termination of the study.

Finally, I think that one needs to balance the need to encourage changes in a study, such as adding an additional review to an existing procedure in order to explore a possible problem. It may be reasonable to proceed with the initial additional review of the scans in a limited number of subjects (to eliminate apparent hazards) and, based on findings from that review then consider the need to have protocol amendments, updates in informed consent, Investigator's Brochure and changes to the FDA-1572 to reflect the independent review facility.

I hope this information is helpful to you.

Sincerely,

Bonnie

Bonnie M. Lee
Associate Director for Human Subject Protection Policy
Good Clinical Practice Program, FDA
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-----Original Message-----
From: [purged]
Sent: Wednesday, May 24, 2006 3:40 PM
To: OC GCP Questions
Subject: FDA GCP Question

Dear FDA:
If per a protocol, a study collects CT scans specifically for tumor assessments, but, based on some unexpected patient adverse events (small population, but seen accross several studies of the same compound), wants to add an additional review for the scans (i.e. looking at the stomach or other specific organs), which would be reviewed only by an independent review facility (nothing done at the investigator site), what would the FDA expect with regards to this needing to be addressed in a protocol amendment?

Since this is only exploratory, and only assessing to see if the increased incidence of the AE may be an issue, could an update to the Statistical Analysis Plan (and/or Data Management Plan), and a Dear Investigator letter to the investigator sites (and IRB), be acceptable?

Also, since it has not yet been determined if this is a safety issue, or any issue at all (besides just being an unexpected incidence of adverse events), would the FDA expect to see an update to the Informed Consent Form (ICF)? I would think that only if there is a determined patient safety issue, or determined updated study information, would an updated ICF be warranted.

Again, this added review to the existing scans is only an exploratory assessment, based on a small patient incidence of an unexpected adverse event.

The bottom line is, if you are going to add an additional review to an existing procedure, which is only exploratory in nature, would the FDA expect to see an amendment to the protocol, or can another method be undertaken?

Thanks.