From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Tuesday, May 23, 2006 3:18 PM
To: **[Redacted]**
Subject: RE: Sub-investigator or not?

Dear Ms. **[Redacted]**:

I apologize for the delay in responding to your question. We are frequently asked who should be listed on the 1572, and it's a question for which there is limited guidance and not always a straightforward answer. Many people do not realize that one of the main purposes of the 1572 is to provide the sponsor with information about the clinical site and investigator qualifications which will enable the sponsor to establish and document that the investigator and site are qualified to conduct the study.

Block #6 asks for the "Names of the subinvestigators (e.g., research fellows, residents, associates) who will be assisting the investigator in the conduct of the investigation(s)." "Subinvestigator" is indirectly defined in the drug and biologics regulations (21 CFR 312.3(b)):

> "Investigator means an individual(s) who actually conduct(s) a clinical investigation (i.e., under whose immediate direction the drug or biologic is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team."

Again, the purpose of block #6 is to capture information about those individuals *who will play a key role in the collection, and interpretation of data, as well as in the conduct of the study itself*. Hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data are generally not meant to be listed in box 6, and so a general statement regarding the participation of staff residents on rotation can be included in item 6.

Whether to list an individual depends on the level of responsibility the individual has in the conduct of the study and in the evaluation of information obtained during the study. If the individual in question has significant study related duties (e.g., explaining the study to subjects, qualifying the study subjects), then the person should be listed on the 1572. If the individual merely ensures and observes that, for example, a consent form is signed by the subject after the principal investigator has explained the study and qualified the subject, then this person would not have to be listed.

Getting back to your original question, I would have to say that the situation that you have described would probably depend on what the study protocol says. Even if a procedure is one generally conducted for medical/diagnostic purposes, there may be specific requirements set forth in the study protocol as to how the procedure should be carried out. Using your example of an endoscopy, the

protocol might require the physician to look for lesions in certain places or measure lesions in a certain way. Consider too, that the study sponsor would need to be aware of who is performing the endoscopies to ensure that the individuals are qualified by training and experience to contribute to the study, particularly if the procedure collects endpoint data for the study. In addition, the sponsor might want to monitor them. In such instances, it would make sense to list the subjects' physicians on the 1572.

On the other hand, there could be a situation in which subjects are required to have a routine followup procedure (e.g., blood or other lab test, routine eye exam) at some point after they last received the test article. To reduce the inconvenience for study subjects who live a long way away from the clinical site, the study protocol may allow each subject's personal physician to perform the test or activity. In such cases, FDA does not view the personal physician as a sub-investigator, and would not expect him/her to be listed on a 1572. Instead, study records should describe the types of tests/activities that may be performed by the subjects' personal physicians, describe the rationale for allowing someone other than the clinical investigator to do so, and note that the results will be provided to the clinical investigator. Each subject's case history should also indicate the contact information for the person who performed the test/activity and the results.

Finally, one last thing to take into consideration when trying to decide if a person should be listed on the 1572 as either an investigator or subinvestigator is the fact that persons listed must disclose information about their financial interests, under FDA's regulations for "Disclosure of Financial Interests by Clinical Investigators" (21 CFR 54). These regulations define "clinical investigator" as any "listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator" (21 CFR 54.2(d). Question 12 of FDA's financial disclosure guidance (http://www.fda.gov/oc/guidance/financialdis.html, specifically addresses this issue.

I'm sorry that I could not give you a simple "yes" or "no" answer, but I hope this gives you some idea about the things that should be taken into consideration.

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: Monday, April 24, 2006 12:06 PM
To: OC GCP Questions
Cc: [Redacted]

Subject: Sub-investigator or not?

Good Morning,

I am well aware of all the questions you have been asked on the topic of sub-investigators but I have been unable to find a specific reference to the below situation. I would greatly appreciate your input on the topic.

There are quite a few clinical trials these days that required complicated procedures as part of the protocol. Many of these procedures, such as endoscopies, are performed by physicians who are not under the direct supervision of the Investigator. These physicians perform the procedures and make the diagnosis per their education and training but are making these as “medical” decisions and not necessarily for the clinical trial. The results are forwarded to the Investigator who then makes ultimate decisions for the protocol.

The question here is this. Should industry be placing these “ancillary physicians/professions” on the 1572 as sub-investigators. There seems to be quite a bit of debate on the subject as results of these procedures can sometimes be the primary endpoint for a study.

Personally, I am not comfortable with placing a person on the 1572 unless he/she is actively participating in decision making for this particular study. I am interested in your views on this topic and would greatly appreciate your input.

Thank you for your assistance,
[Redacted]