From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Thursday, November 09, 2006 9:46 AM
To: '**[Redacted]**
Subject: RE: independent blinded reviewers

Dear Mr. **[Redacted]**,

I don't think there is a single "right" answer to your question. There is certainly no harm in having a "Medical Doctor" in charge, and having the individual sign a 1572 to ensure that they are aware of and committed to complying with FDA's regulations for conducting their activities related to the clinical trial, particularly if the readings ("outcomes") are intended to support a primary efficacy endpoint (and medical/clinical judgment is required).

If the sponsor has contracted with the facility that is performing the blinded readings, then I suppose you could list it on the 1571 (block 12, item 6c); if the clinical investigator secured the services of the facility, then it could be listed on the 1572 under block #4. In any case, the information needs to be documented somewhere in the clinical trial records, so that if FDA wishes to inspect them, we could do so.

Does this help?

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

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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.

-----Original Message-----
From: **[Redacted]**
Sent: Wednesday, November 08, 2006 4:16 PM
To: OC GCP Questions
Subject: RE: independent blinded reviewers

Thank you Ms. Hommel for you quick response. This is helpful but if possible, may I clarify my problem and maybe you could better understand my questions...

Hypothetical situation, of course... But, if a site is selected as a "core lab" for blinded readings of MRI, for example, images for the efficacy of a Phase III

study, should the site be treated as an investigator site (meaning that I would require IRB approval for the blinded reading, a Medical Doctor to be in charge, a 1572, CVs, Debarment certificates, ect) or can the site be treated as a laboratory (like an off site clinical lab), and if so who's 1572 or 1571 would they be listed on? Since the images are going from the site of acquirement to the Sponsor and then to the Core Lab for a blinded reading, then I would not suspect that it would belong on the site of acquirement? Hope this makes sense...

#2, If you suggest that the site be treated as an Investigator site, would it make a difference if there was a medical judgment for the outcome of the blinded reads or if the blinded reads we actually considered just conducting a analysis function rather than a medical judgment reading, and if so, is there an appropriate title to give to this type of function instead of Independent Blinded Readers (which again makes me believe that a medical judgment is needed).

Thank you again for your help, I hope these are not ignorant questions and of course I am just looking for guidance and not judgment of an issue.

[Redacted]

From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Wed 11/8/2006 3:29 PM
To: **[Redacted]**
Cc: CDER DRUG INFO
Subject: RE: independent blinded reviewers

Dear Mr. **[Redacted]**:

Your questions were forwarded to me for a response.

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 a particular 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):

"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." 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s)."

The purpose of Block #6 is to capture information about individuals who, as

part of an investigative team, will be assisting the investigator and who make a direct and significant contribution to the data. The decision to list an individual in Block #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant study-related duties). In general, if an individual is directly involved in the treatment or evaluation of research subjects, that person should be listed on the 1572. For this reason, it makes sense to list an individual who will be reviewing ECG tracings or x-ray films on the 1572 in Block #6 as a sub-investigator for the study.

I'm not sure I completely understand your second question, but I think you may be asking how much oversight needs to be given to study activities that are performed by parties that are not under the direct control of the clinical investigator. For example, clinical chemistry laboratories, radiologic assessments, and electrocardiograms may be done by a central independent laboratory retained by the sponsor. Under these arrangements, the central laboratory usually provides the test results directly to the sponsor and to the clinical investigator. Because the activities of these parties are critical to the outcome of the study, and because the sponsor retains the services of the laboratory, the sponsor is responsible for seeing that these parties are fulfilling their responsibilities for the study.

Less frequently, a study may require that clinical investigators arrange to obtain information critical to the study that cannot be obtained at the clinical investigator's facility. For example, if the study protocol requires testing with special equipment or expertise not available at the clinical investigator's facility, then the investigator might make arrangements for someone outside the facility to perform the test. In this instance, the results are provided directly to only the clinical investigator, who then submits the information to the sponsor. Where such assessments are retained by the investigator, the investigator should takes steps to ensure that the facility is adequate (e.g., has the required certifications or licenses). The investigator may also institute procedures to ensure the integrity of data and records obtained from the party providing the information (e.g., a process to ensure that records identified as coming from the party are authentic). Procedures are particularly important when assessments are crucial to the evaluation of the efficacy or safety of an intervention, or when deciding to exclude subjects who would be exposed to unreasonable risk.

Clinical investigators should carefully review the reports from such external sources for results that are inconsistent with clinical presentation. To the extent feasible and considering the specifics of study design, the clinical investigator should evaluate whether results appear reasonable, individually and in aggregate. If clinical investigators detect possible errors or suspect that results from a central laboratory might be questionable, the investigator should contact the sponsor immediately.

I hope this is helpful.

Sincerely,

Carolyn Hommel
Consumer Safety Officer
Good Clinical Practice Program
Office of Science and Health Coordination

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-----Original Message-----
From: **[Redacted]**
Sent: Monday, November 06, 2006 11:09 AM
To: CDER DRUG INFO
Subject: DrugInfo Comment Form FDA/CDER Site

Name: **[Redacted]**

E-Mail: **[Redacted]**

Comments: Hi, hope you can help... I have been searching guidance documents and CFR and have not been able to find any information on Independent blinded readings... Here are my questions...

1) Does and independent blinded reviewers (imaging modalities) need IRB approval and a 1572 and other documents such as required by a site conducting clinical research.

2) Is there a difference between a site conducting independent blinded readings by a radiologist and a site that would be producing independent blinded analysis? Does this analysis need to be approved by a MD?

Thanks You
[Redacted]