From: Hommel, Carolyn - OC on behalf of OC GCP Questions
Sent: Wednesday, April 19, 2006 10:42 AM
To: [Redacted]
Subject: RE: Clinical Sites with Satellite Sites

Dear [Redacted]:

Your questions were forwarded to me for a response.

- Is there any guidance on the number of satellites that a PI may have (I have heard that there may be as many as 30 to 50) or how far distant from the PI?

Answer: There is nothing in FDA's regulations that specifically precludes an investigator from overseeing one or more "satellite" sites. However, the practice that you described (i.e., 30-50 "satellite sites") raises other concerns. If such sites are geographically remote, how will the investigator "personally conduct or supervise the described investigations" as he commits to doing when he signs the 1572? How will he/she ensure that the study is being conducted according to the study protocol and investigational plan, that all observations related to the study are appropriately documented, that all study staff are complying with the requirements for the conduct of such studies? The scenario that you have described has the potential to generate confusion as to who is responsible for the study and a lot of finger-pointing if anything goes wrong.

FDA's official guidance, the ICH E6, Good Clinical Practice: Consolidated Guidance, defines "Investigator," as "A person responsible for the conduct of the clinical trial ***at a trial site***..." [See Section 1.34; emphasis added] Thus, in keeping with the ICH guidance, you might consider having an investigator at each site sign his/her own 1572.

- Does the PI need to physically visit satellite sites to ensure oversight?

Answer: Your question raises another: How will the investigator "personally conduct or supervise" the conduct of the study, if he/she is not physically at the site while study activities are going on and never goes there? Again, we suggest that you consider the recommendation of the ICH guidance, i.e., by having a designated investigator who is responsible for the conduct of the clinical trial ***at each site***.

- Can the IRB at the PI's institution take responsibility for the satellites sites without a cooperative research agreement with local IRBs?

Answer: This would generally not be in keeping with Good Clinical Practice.

In March, FDA issued guidance for industry, "Utilizing a Centralized IRB Review Process in Multi-Center Clinical Trials." The guidance recommends that review of studies using a centralized IRB be documented in writing so that all parties (Central IRB, local IRB(s), investigators, institutions) are all aware of each other's respective responsibilities for the study. I have pasted an excerpt from that guidance into this e-mail for your convenience:

"A. Documenting Agreements

"If an institution, its IRB, and a central IRB agree (under 21 CFR 56.114) to participate in a centralized IRB review process, they should document that action in an agreement signed by the parties. IRBs should report this action to the investigator and the institution, for example, by providing copies of the agreement to the investigator, and the institution....If the agreement apportions IRB review responsibilities between a central IRB and the institution's IRB, the agreement should delineate the specific responsibilities of the central IRB and the institution's IRB for the initial and continuing review of the study. "

You may find it helpful to review this document in its entirety. There is a link on FDA's Good Clinical Practice website: http://www.fda.gov/oc/gcp; once at the site, click on "Guidances and Information Sheets" in the middle column, and scroll down the list.

- Should the PI be licensed to practice in the states where his satellites are located (assuming he is licensed in the state where his institution is located)?

Answer: FDA regulations for the selection of investigators state, "A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug" [21 CFR 312.52(a)]. The sponsor is also required to obtain a "curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation." [See 21 CFR 312.52(b)(2).]

Although FDA regulations do not mention licensure, in general, any study personnel carrying out a study should be performing only those study functions that are within the scope of their professional license(s). As you know, this varies from jurisdiction to jurisdiction and is regulated by the States. Thus, the professional licensing authority in the State(s) in which the study is taking place would have the final word on whether physicians who are not licensed in the U.S. may administer investigational drugs to human study subjects or perform other aspects of clinical research.

- Is there any concern that the PI's institution will receive all study drug then redistribute it to the satellite sites? What would the FDA expect to see for documentation of drug accountability under such a program?

Answer: The investigator is responsible for ensuring control of the investigational product.

21 CFR 312.61 states, "An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it."

21 CFR 312.62(a) states, "An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by

subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59."

The regulations, as you can see, are fairly general. Thus, sites have the flexibility to establish their own procedures and records related to receiving, dispensing, and disposing of supplies of investigational drugs. Investigators/sites need to be ensure that the investigational drug is provided only to those individuals who are authorized to receive it, administered only to study subjects under their personal supervision or the supervision of subinvestigators responsible to the investigator, and that investigational drug supplies are appropriately tracked.

- How would the FDA inspect such a site? Would each satellite be considered a separate entity or would all 30 – 50 sites be included in one inspection of the PI?

Answer: FDA's inspectional procedures are contained in the Compliance Program Guidance Manual. There is a link to the CPGM on FDA's Good Clinical Practice website: http://www.fda.gov/oc/gcp. Once there, click on "Bioresearch Monitoring Program" in the middle column. In general, when FDA inspects a study, the FDA investigator usually needs to speak to the actual individuals who carried out study related tasks at that site.

- If SAEs occurred at a satellite site but were not reported to the PI, IRB, or sponsor, would the PI still be responsible or would the FDA hold the subinvestigator at the satellite site accountable?

Answer: The person who signs the 1572 is responsible for the conduct of the study, including the conduct of the subinvestigators and other study staff who report to him. Thus, we again suggest that you consider the recommendation of the ICH guidance, i.e., by having a designated individual who is responsible for the conduct of the clinical trial ***at each site***, and have that individual sign his/her own 1572.

- Where should the CRFs be located – with the PI or at the offices where subjects are seen?

Answer: As stated above, when FDA inspects a study, the FDA investigator generally needs to speak to the individuals who are responsible for seeing the subjects and recording all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. The records should be available wherever the individuals who created them are located so that if there are any questions, the FDA investigator can direct them to the responsible individuals.

- What should the PI do to ensure that the source documentation at the satellites is adequate and retained for the required time period? Especially if the satellites are in different states, there may be different requirements for retention.

Answer: FDA's regulatory requirements for retaining study records are found at 21 CFR 312.62(c): "An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified."

As you can see, the regulations are very general, thus giving the investigators and sites the flexibility to develop their own processes and procedures for preserving and ensuring access to study records.

- Does the sponsor fulfill its obligation to provide the PI with the information needed to conduct the trial if all communications are sent directly to the PI; or does the FDA expect the sponsor to provide communications directly to the subinvestigators at the satellite sites?

Answer: Sponsors are required, under 21 CFR 312.55, to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports, or letters to clinical investigators or other appropriate means."

To avoid any confusion, we suggest following the approach in the ICH guidance (as stated above), and consider having an investigator who is responsible for the conduct of the clinical trial ***at each site***. That way, the sponsor can send information directly to all investigators who need to be informed about the investigational product and verify receipt, as appropriate.

- Is it acceptable for monitoring to be performed solely at the PI's institution if copies of source and CRFs for the satellites are there?

Answer: The sponsor is responsible for "ensuring proper monitoring of the investigation(s)" [See 21 CFR 312.50.] The sponsor should have an appropriate plan to ensure that all sites are appropriately and adequately monitored.

- In terms of study bias, is it reduced through the use of satellites or increased because all the subjects at the satellites are under the evaluation of the PI?

Answer: This should best be addressed by a statistician in the context of the specific protocol. Regardless of the answer, you need to ensure that there is appropriate supervision and oversight for the conduct of the study at all sites.

Sincerely,

Carolyn Hommel
Consumer Safety Officer

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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.

From: [Redacted]
Sent: Friday, April 07, 2006 4:29 PM
To: OC GCP Questions
Subject: Clincial Sites with Satellite Sites

Does the FDA provide any guidance on "satellite sites". These are medical offices often distant from the location of the PI (they can be in different states) but are listed on the FDA-1572 for the PI as locations where the study will be conducted. From the FDA's point of view:

- Is there any guidance on the number of satellites that a PI may have (I have heard that there may be as many as 30 to 50) or how far distant from the PI?
- Does the PI need to physically visit satellite sites to ensure oversight?
- Can the IRB at the PI's institution take responsibility for the satellites sites without a cooperative research agreement with local IRBs?
- Should the PI be licensed to practice in the states where his satellites are located (assuming he is licensed in the state where his institution is located)?
- Is there any concern that the PI's institution will receive all study drug then redistribute it to the satellite sites? What would the FDA expect to see for documentation of drug accountability under such a program?
- How would the FDA inspect such a site? Would each satellite be considered a separate entity or would all 30 – 50 sites be included in one inspection of the PI?
- If SAEs occurred at a satellite site but were not reported to the PI, IRB, or sponsor, would the PI still be responsible or would the FDA hold the subinvestigator at the satellite site accountable?
- Where should the CRFs be located – with the PI or at the offices where subjects are seen?
- What should the PI do to ensure that the source documentation at the satellites is adequate and retained for the required time period? Especially if the satellites are in different states, there may be different requirements for retention.
- Does the sponsor fulfill its obligation to provide the PI with the information needed to conduct the trial if all communications are sent directly to the PI; or does the FDA expect the sponsor to provide communications directly to the subinvestigators at the satellite sites?
- Is it acceptable for monitoring to be performed solely at the PI's institution if copies of source and CRFs for the satellites are there?

- In terms of study bias, is it reduced through the use of satellites or increased because all the subjects at the satellites are under the evaluation of the PI?

I think this set up for clinical research may be more common among federally funded research than for industry sponsored trials.

I appreciate you attention to these questions. As a [Redacted] I can see the risks inherent in the satellite scenario. However, unless FDA has guidance on or can provide examples of citations for deficiencies in such an arrangement, industry will be pressured to accept this scenario when working with sites more familiar with NCI/NIH studies. Any guidance or information you can provide would be greatly appreciated.

Thank you,

[Redacted]