From: Woollen, Stan - OC on behalf of OC GCP Questions
Sent: Friday, July 16, 2004 2:50 PM
To: [Redacted]
Subject: RE: some general GCP queries
Dear [Redacted],

I've been asked to reply to your questions in the absence of Bonnie Lee. I've copied each into the body of my response to ensure that I address each in turn.

1. Q i"f the monitoring report itself is used as a measure to ensure corrective actions at the site by sending the monitoring report directly to the site and stored in the ISF, would this be considered an anomaly and significant finding by an auditor ?"

A. If I understand your question correctly you are asking if an auditor would object to finding a monitoring report in the investigator's study file. No, this is not an anomaly and would not be objectionable. It is quite common for sponsors to provide monitoring reports to the investigator site and these are usually retained in the study file. FDA auditors will often look for such reports during their inspections as evidence that the sponsor has fulfilled their obligation to ensure adequate monitoring.

You may also be concerned that objectionable findings reported by the monitor might also be cited by the auditor. If there is evidence that appropriate corrective action was taken to remedy the monitor's finding it is not likely that the monitor's report alone would serve to support an objectionable finding by the auditor. However, if during the course of the audit, the auditor independently discovered a regulatory deviation or observed that a regulatory deviation cited by the monitor had not been corrected and continued throughout the study, this might be cited as objectionable by the auditor.

2. Q. "Would you please elaborate as to who is considered as a competent person ? Pl. give some examples."

A. It is a matter of State or local law, as to who would be considered competent. Therefore I can't readily answer this question. Some examples of criteria for establishing competency would be the age of the individual and their mental capacity. However, the individual obtaining consent should consult with the appropriate legal authority if there is any doubt about the competency of an individual to give consent.

3. Q. "Can LAR who is a literate sign and date in the space provided for the subject in the ICF, if the subject is illeterate or not in a position to sign thereby representing him ?"

A. As Bonnie Lee described in her answer # 2 below, a LAR is required to sign the consent form, in lieu of the individual, ONLY if the subject is not competent to do so. Just because a subject is illiterate does not make them incompetent to sign (i.e. make their mark) upon a consent form, therefore the literacy of the subject in not relevant. When it is appropriate for a LAR to sign for an incompetent subject, they should sign the form in a manner acceptable to the IRB and the appropriate legal authority. FDA has no regulatory requirement as to how the LAR is to affix their signature only that the signature be dated. It is customary when a LAR signs that the consent form should indicate they are signing for the subject in their capacity as a LAR.

I am not sure I understand the last phrase of your question where you refer to the subject as "not in a position to sign" if you are referring to a person who can understand and comprehend spoken English, but is physically unable to talk or write, we do have some guidance on this topic in our information sheets. You can find the information sheets on our website at

http://www.fda.gov/oc/ohrt/irbs/default.htm. In the case you are referring to, such a subject could be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

4.Q. "Who all the persons may be considered as " impartial witness " ? Pl. give some examples."

A. Impartial has its common meaning of a party who is not biased in favor of a particular outcome. An impartial third party witness for example could be someone who is not involved in anyway with the study and has no vested interest in the outcome of the study, or the subject's participation. You should consult with the IRB who has authority over the site on this issue.

5. Q. "who all the persons may be considered as "LAR".

A. Much like the determination of competency as discussed in question #2 above, the LAR must meet the legal requirements within the jurisdiction where the study is to take place. Since this is a matter of State or local law, who would be considered a LAR can vary from state to state. The individual obtaining consent should consult with the appropriate legal authority if there is any doubt about the LAR's qualifications.

6. Q. "Is the person administering informed consent needs to be a doctor always ? or any person designated by the investigator who is well versed with the study would do ?"

A. This is addressed in our information sheets as follows. The person who conducts the consent interview should be knowledgeable about the study and able to answer questions. FDA does not specify who this individual should be. Some sponsors and some IRBs require the clinical investigator to personally conduct the consent interview. However, if someone other than the clinical investigator conducts the interview and obtains consent, this responsibility should be formally delegated by the clinical investigator and the person so delegated should have received appropriate training to perform this activity.

7.Q. "Is documentation required to show that a signed copy of the informed consent is given to the subject or LAR before study participation ? or just giving a copy will do without specific records. If to be documented, can investigator/sub investigator who takes consent certify that it was given before subject's study participation ? will it suffice ?"

A. On Nov. 5, 1996 The Food and Drug Administration (FDA) amended its informed consent regulations to require that the consent form signed by the subject or the subject's legally authorized representative, be dated by the subject or the subject's legally authorized representative at the time consent is given. FDA is also amended its regulation on case histories to clarify what adequate case histories include and to clarify that the

case histories must document that informed consent was
obtained prior to participation in a study. FDA took this action in response to problems the agency has had on occasion verifying that informed consent was obtained from a research subject prior to participation in a study because the consent document was not dated and other verification was not contained in the individual's case history documentation. The agency believes that by explicitly requiring that the consent form be dated at the time it is signed and requiring the case history to document that consent was obtained prior to participation in a study, the agency will be able to help ensure that informed consent was, in fact, obtained prior to entry into the study as required by FDA regulations.

For a very comprehensive discussion of this issue and FDA's position, please refer to the preamble to the Nov. 5, 1996 amendment to 21 CFR 50 found on our website at http://www.fda.gov/OHRMS/DOCKETS/98fr/11059601.txt

8. Q. "The informed consent form to be used by the subject is to be approved by the IRB. Is it enough if IRB say in its approval letter for the study that they reviewed all the study documents submitted including ICF and approved. ? Do each informed consent form to be used by the subject has to bear the stamp of IRB ?"

A. As long as the study records clearly document IRB approval of the consent form in use, study sites are free to use whatever method they chose to accomplish this. Many IRBs do chose to require an IRB stamp on the consent form, while others simply approve the consent form during their initial approval and during subsequent continuing review require the CI to submit the current consent form in use to verify that it still complies with the IRB's requirements. This review is usually reflected in the IRB records and procedures.

I hope this information addresses the issues raised in your e-mail to Bonnie and is helpful.

Sincerely yours,

Stan W. Woollen
Associate Director for Bioresearch Monitoring
Good Clinical Practice Programs
OSHC, Office of the Commissioner

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: Thursday, July 08, 2004 6:30 AM
To: GCPQuestions@OC.FDA.GOV
Subject: RE: some general GCP queries
Importance: High

Dear Bonnie,

Thank you very much for your response. Can I ask you some more queries on the same topic. I would be highly thankful to you if you can kindly clarify the same.

"if the monitoring report itself is used as a measure to ensure corrective actions at the site by sending the monitoring report directly to the site and stored in [Redacted], would this be considered an anomaly and significant finding by an auditor ?" .

Would you please elaborate as to who is considered as a competent person ? Pl. give some examples.

Can LAR who is a literate sign and date in the space provided for the subject in the ICF, if the subject is illeterate or not in a position to sign thereby representing him ?

Who all the persons may be considered as " impartial witness " ? Pl. give some examples.

who all the persons may be considered as "LAR".

Is the person administering informed consent needs to be a doctor always ? or any person designated by the investigator who is well versed with the study would do ?

Is documentation required to show that a signed copy of the informed consent is given to the subject or LAR before study participation ? or just giving a copy will do without specific records. If to be documented, can investigator/sub investigator who takes consent certify that it was given before subject's study participation ? will it suffice ?

The informed consent form to be used by the subject is to be approved by the IRB. Is it enough if IRB say in its approval letter for the study that they reviewed all the study documents submitted including ICF and approved. ? Do each informed consent form to be used by the subject has to bear the stamp of IRB ?

Thanking you in anticipation,

Warm regards,

[Redacted]

[Redacted]
---Original Message-----
From: Lee, Bonnie [mailto:BLee@OC.FDA.GOV]**On Behalf Of** OC GCP Questions
Sent: Wednesday, June 30, 2004 9:45 PM
To: [Redacted]
Subject: RE: some general GCP queries

Dear [Redacted],

You have asked some interesting questions. Let me try to answer each in turn.

1. FDA regulations do not explicitly address monitoring reports. Although there is some mention in the International Conference on Harmonisation Good Clinical Practice (E6) Consolidated Guidance, it does not address the issue of providing a copy of the monitoring report to the investigator. From a quality control standpoint, however, it is important that for monitoring to be effective, the finding of any deficiencies or deviations be communicated to the clinical investigator and study site.

2. A competent person who does not read and write can enroll in a study following an oral presentation of the information contained in the consent form by "make his/her mark" on the informed consent document when consistent with applicable (State and other) law. There should also be an impartial witness to the entire consent process who should sign the consent document. This assumes that the subject is competent in which case there is no role designated in the regulations for a legally authorized representative (LAR). The LAR would be needed if the subject were NOT competent. A thumb impression of the subject is not required. The LAR could sign as the witness for the subject if the IRB agrees that such a person is impartial; if not, then another person should be sought for this role.

3. Our regulations do not specifically address this question although they assume a certain sovereignty of the IRB (see, for example, 21 CFR 56.112). I think that we would question why the sponsor would want to change the IEC--is it "for cause" (that is, concern that the IRB is not in compliance with FDA's regulations) or because the investigator has moved to another site? Those would seem to be legitimate reasons. I can think of other reasons that we might consider suspect and inappropriate.

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

-----Original Message-----
From: [Redacted]
Sent: Thursday, June 24, 2004 2:34 AM
To: gcpquestions@oc.fda.gov
Subject: some general GCP queries
Importance: High

I am [Redacted] and have a query on the above matter.

1. In what circumstances or scenario, the monitoring visit reports can be provided as such to the investigator or documented in the investigator site file ?

can the monitoring visit reports be documented at the investigator site at all ?

2. For informed consent documentation, where the subject is illiterate, can subject's legally acceptable representative if literate , can sign and date the document on behalf of the subject? in addtion, is

the thumb impression of the subject required to be taken ?

can a family member (LAR)of the subject sign as a witness for an illiterate subject ?
does the family member of the subject falls under "an impartial witness" ?

3. can an independent ethics committee be changed by the sponsor, once the review process is completed for study approval to that of another IEC for any reasons ? before the study commencement?

awaiting your response soon,

Thanks & regards,

[Redacted]