From: OC GCP Questions
To: [redacted]
Subject: RE: CORRECTIONS TO SIGNED ICF
Date: Thursday, February 26, 2015 11:23:00 AM
Attachments: [redacted]

Dear [redacted] -

Thank you for your question. If I correctly understand the scenario you describe, it sounds as if a sponsor/CRO CRA instructed a PI/site to make a change to the IRB-approved, signed ICF on file at the PI's site. As you indicated, this resulted in the subject's copy of the ICF being different than the copy in the PI files.

The FDA regulations do not specifically address how to make corrections or changes to an IRB-approved document such as the ICF. When the regulations are silent, IRBs, institutions, sponsors, CROs, and investigators are free to develop their own procedures and practices as long as applicable regulatory requirements are met. However, there are some other FDA regulations mentioned below that should be taken into consideration when determining the procedures and practices for making corrections or changes to IRB-approved documents, such as the ICF.

According to the FDA IRB regulations at 21 CFR 56.111(a)(4) and (5) – see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.111, and copied below for reference:

> Sec. 56.111 Criteria for IRB approval of research.
>
> (a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:
>
> (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.
>
> (5) Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.

The IRB typically issues the IRB-approved ICF to be used by the PI/site. IRB-approved documents are usually not altered without a request for a change submitted to the IRB first for consideration.

Also, according to the IRB regulations at 21 CFR 56.108(a)(3) and (4) – see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.108, and copied below for reference:

> Sec. 56.108 IRB functions and operations.
>
> **In order to fulfill the requirements of these regulations, each IRB shall:**
>
> **(a) Follow written procedures:** (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; **(3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.**

If the CRA wanted to change the IRB-approved ICF (i.e., to add the second name of the PI), did the PI consult his/her IRB about making this change? Is this a change that will need to be made to all ICFs at that site? IRB's are required to follow written procedures for ensuring prompt reporting of changes in the research and likely have a written procedure about the process for making **any** changes to an IRB-approved document, such as the ICF. It is important to know and follow the IRB requirements. Again, IRB-approved documents are usually not altered without a request for a change submitted to the IRB first for consideration.

Does the PI/site have any SOPs that might address how they are supposed to handle documenting corrections or changes to IRB-approved documents? Is the PI/site affiliated with an institution that has any SOPs on documenting corrections or changes to IRB-approved documents? Does the sponsor or CRO have any SOPs on how to handle documenting corrections or changes to IRB-approved documents that should have been followed?

Also, the FDA IND regulations for investigator responsibilities at 21 CFR 312.62(b) – see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62, and copied below for reference, require:

> Sec. 312.62 Investigator recordkeeping and record retention.
>
> (b) Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

I suggest that you discuss this particular issue internally with your management to find out what the sponsor/CRO company expectations are for making corrections or changes to IRB-approved documents, and that you consult the IRB about what requirements they have for making corrections or changes to any IRB-approved documents. If SOPs do not exist, you may consider developing SOPs to address company expectations for making corrections and changes, especially to IRB-approved documents. This should help minimize any inconsistencies.

Making a change to an IRB-approved document without consulting the IRB, especially when this change results in differences across copies of the same document, is not recommended.

I hope this information is useful. If you need further information and/or have additional questions, please feel free to contact us at the official GCP mailbox, gcp.questions@fda.hhs.gov. You may also find it useful to access the set of redacted GCP e-mails found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm since we find that many questions and concerns are repeated over time.

Best Regards,

Janet

Janet Donnelly, RAC, CIP
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and Drug Administration

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From: [redacted]
Sent: Tuesday, February 24, 2015 12:49 PM
To: OC GCP Questions
Subject: CORRECTIONS TO SIGNED ICF

DEAR FDA:

A CRA commented to me that she requested to one of his sites to make some GCP corrections to an already signed ICF, the correction consisted adding the second name of PI (but the ICF process was correctly taken). The PI performed the corrections but the subject's ICF remains the same so: we have two ICFs signed the same date but not identical. I consider that corrections to a signed ICF do not make sense because it results in two documents with different information. I think that this request of correction could result in more and more extra work for the site and a audit/inspection finding.

¿Could you please tell me your opinion about it?

Kind regards

[redacted]