From: OC GCP Questions
To: [redacted]
Subject: How to proceed when ICF has been signed and there are findings
Date: Tuesday, September 06, 2016 12:31:00 PM
Attachments: [redacted]

Good afternoon --

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 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 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 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 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.

Generally speaking the steps described in ICH E6 4.9.3 represent an acceptable method to make changes or corrections in study documents. The FDA recognized ICH E6: Good Clinical Practice: Consolidated Guidance, available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf, does include the following recommendations:

Section 4.9.3: "Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections."

Generally, the change should be crossed out with a single line, initialed, dated in real time, and explained by writing “error” without obscuring the original document.

For more complicated corrections, a note to file might be appropriate. Document your corrections with a note to file, including how you followed up with the subject.

You also may want to develop a standard operating procedure (SOP) for all study staff to follow with regard to corrections. This will minimize inconsistencies. Make sure that the corrections you describe are in line with your institution's policies and procedures.

If you and your IRB decide that re-consenting is necessary, FDA regulations do not dictate the time limit on the consenting process. Whether or not a "reconsent" is needed depends upon the nature of the change in the study protocol or information about the study that warranted the change. For example, if the informed consent was updated because new adverse effects (AEs) were detected at some study sites, it is extremely important to convey that information to all study subjects. Depending upon the nature and/or severity of the AEs, some existing subjects may choose to discontinue their participation in the study. Therefore, capturing the renewed consent of those who choose to remain in the study is also significant.

However, if the change is due to a new test, procedure, or treatment that was added to the study protocol and only new study subjects will be subject to the addition(s), then it would not be necessary to inform existing study subjects.

When considering reconsenting -- reconsenting the subject shows respect for the subject and, because the subject may not remember all of the information previously provided about the study, repeating the informed consent process and reviewing the information in the consent form with the subject will allow the subject the opportunity to refresh his/her memory about what participation in the trial will entail, the risks that may be involved, who to contact in case he/she has any adverse experiences, etc., and to ask any questions that he/she may have.

I hope this information is helpful. Please contact us again at gcp.questions@fda.hhs.gov should you have additional questions.

Kind regards,

Doreen M. Kezer, MSN
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Office of Good Clinical Practice
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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: Monday, September 05, 2016 2:47 PM
To: OC GCP Questions
Subject: How to proceed when ICF has been signed and there are findings

Dear GCP Group:
Please receive my best regards.

I have seen different approach regarding how to proceed when Informed Consent has not been filled out by patient/subject as expected. Let me provide some examples.

Findings in an elderly population: (older than 70 years old)

Subject personally include his/her name and signature but spaces for ID # and date where included by a relative. Identification of relative is possible since per local regulation all ICF should include two witnesses.

Subject personally include his/her name, signature, date and ID but the handwriting was not clear at all, therefore the relative included above this information clear information.Identification of relative is possible since per local regulation all ICF should include two witnesses.

A. Would be acceptable from regulatory point of view that subject make a note to clarify that he/she authorized the relative to include this information, sign and date within the same previous signed ICF.

B. Would be necessary to re-sign a new consent form?

C. Could be acceptable to create a note to File, sign and date by PI and by subject?

I have search and found some articles regarding re-consent vs re-sign and for some errors as giving subject the wrong version, unapproved one, however the kind of findings reported above wont trigger the need to provide new clean Informed Consent (same version subject signed before as understood there is still applicable) but would be possible to proceed as scenarios A and C.

However, I would like to be sure about Regulatory Agency point of view.

Thanks in advance,

[redacted]