From: OC GCP Questions
To: [redacted]
Subject: Multiple Questions
Date: Tuesday, April 07, 2015 11:44:34 AM

Good morning ---

With regard to IRB approval, the FDA regulations at 21 CFR 56.109(a) state:

Sec. 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

The regulations at 21 CFR 56.109(e) state:

(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

FDA regulations do not specifically advise how an IRB will document the review or change in research. When the regulations are silent, IRBs and institutions are free to develop their own procedures and practices as long as applicable regulatory requirements are met.

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.

Many institutions and sites are going to a fully electronic record system. Your EMR can be your source record. The clinical investigator would have to maintain some sort of source documents at his/her site. The data should not be just entered at the sponsor site.

You may also want to look at FDA's Compliance Program Guidance Manual (CPGM) for the FDA inspection of clinical investigators during a bioresearch monitoring (BIMO) inspection of a clinical study site, available at: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm
In particular, you may want to review Part III, Inspectional, which identifies some of the things an FDA

investigator will look for during a clinical investigator site inspection.

ICH E-6 Good Clinical Practice: Consolidated Guidance
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf
Please see this guidance for definitions for "source data" and "source document":

"1.51 Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."
"1.52 Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

During an FDA inspection regarding medical records of study subjects, monitors and auditors will want to at least spot check the completeness of these records at the source which is the subject's chart/medical record. How they view them is at the sponsor or clinical investigator discretion however. Either looking over the shoulder of a study staff member or having limited access to the medical records is common.

The reason at least a spot check is necessary is that the records can be selectively copied. So even though they are certified copies they may not be complete records. The monitor/auditor is checking to ensure that study inclusion/exclusion are met and that there are no concomitant issues that would preclude the individual's participation in the study or confound the results.

In general, during an inspection FDA usually reviews original (source) records or certified copies of clinical trial records. For example, during an inspection of a clinical investigator (CI), the FDA investigator will evaluate the CI's practices and procedures to determine compliance with applicable regulations. Quite often CIs maintain copies of certain records in their study files, e.g., records from a hospital or other institution that must maintain the originals. FDA refers to these as shadow files. While it is acceptable to keep shadow files in the study records, should FDA conduct a bioresearch monitoring (BIMO) inspection of the study in question, the FDA investigator will expect to review at least a portion of the original source documents for such shadow files to verify their authenticity, even if the copies in the shadow files are certified as authentic copies.

The guidances listed below might be helpful to you.
Part 11 –Electronic Records --
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf

Computerized Systems Used in Clinical Investigations –
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf

Electronic Source Data in Clinical Investigations –
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf
This document includes information related to the creation and maintenance of electronic case report forms(eCRF). It describes and electronic medical record (EMR) as a possible data originator for an eCRF. However, section IV. of the document states that, although adequate controls need to be in place to ensure confidence in the reliability, quality and integrity of electronic source data, performance standards for EMRs may be regulated by other authorities and FDA does not intend to assess compliance of EMRs with part 11.

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

Kind regards,

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From: [redacted]
Sent: Friday, April 03, 2015 9:48 PM
To: OC GCP Questions
Subject: Multiple Questions

I have a few questions that I need clarified:

I have read the Guidance documents on Informed Consent multiple times. I have read that the IRB has to review consents and the need to reconsent subjects and release an official statement. Here is the scenario:

My Institution utilizes an electronic system that research staff input data about a study. This information is reviewed by IRB staff prior to going to the IRB Board to determine if additional information is needed. In the area for informed consent, the staff is asked if the protocol contains new information and whether subjects have to be reconsented. If the study staff answers that subjects do not have to be reconsented, this is sufficient and reconsent is "waived". It was my understanding that the IRB Board has to review the changes during an amendment and make the determination for reconsent - not the study personnel during data entry. The IRB was asked this question and the response was that a "waiver of reconsent" was not a thing and that the data entry was sufficient, but that leaves no statement in written form via a letter from the IRB Board as to the approval of a waiver or the guidelines of when a subject does not have to be reconsented. Sometimes the change is minor in the consent, but with a new ICF released with that change, having directive directly from the IRB instead of a staff's call seems to make more sense. Can you advise?

Next, source documents. There are statements that a sponsors system can be considered a source document if the entry of the data is direct. I have argued that the Investigator is required to maintain case histories at the Investigational site and the sponsor eCRF system is not the PI's site. If we only enter it into the sponsor database, how are we verifying the data that we have entered as it is not in our medical records or binders? I know what source documents are and what case histories are but am I misunderstanding the requirement of the documentation being maintained at the site level? I have been told that I am misinterpreting the regulations.

I appreciate your help.

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