From: OC GCP Questions
To: [redacted]
Subject: Several questions
Date: Wednesday, March 25, 2015 11:39:53 AM

Good morning --

FDA's regulations at 21 CFR parts 50 and 56 (concerning informed consent and IRBs) primarily discuss documentation of informed consent in terms of the subject, or the subject's legally authorized representative, signing the written consent form. FDA's regulations specific to drug and biologic studies (21 CFR part 312) and device studies (21 CFR part 812) require that information be maintained in subject's case histories, including requirements that "Case histories include the case report forms and supporting data including, for example, signed and dated consent forms" and "The case history for each individual shall document that informed consent was obtained prior to participation in the study." See 21 CFR 312.62(b) for drug and biologic studies and 21 CFR 812.140(a)(3) for device studies. If informed consent is obtained on the same day the subject begins participation in the study, it would be important to document that consent was obtained prior to participation.

There may be other cases where additional documentation about the informed consent process should be considered. For example, enrollment of a subject who is unable to read the consent form due to illiteracy or visual impairment; a subject who wishes to consent but is unable to sign the consent form due to a physical impairment; or a subject with impaired consent capacity for whom a legally authorized representative provides consent. In such situations, additional information may be helpful in documenting the informed consent process.

You may also find it helpful to review FDA's Compliance Program Guidance Manual for FDA Staff for Bioresearch Monitoring inspections of Clinical Investigators, available at http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm. This document includes the following directions, pertaining to informed consent, to FDA investigators conducting clinical investigator bioresearch monitoring inspections:

PART III – INSPECTIONAL

F. HUMAN SUBJECTS' RECORDS

1. Informed Consent
a. Describe the informed consent process. For the study being inspected, include the following information:
i. Who (investigator, nurse, study coordinator, etc.) explained the investigational study and consent document to prospective study subjects, and was it provided in a language understandable to each subject?
ii. How did the informed consent process take place? (e.g., was this explanation given orally, by video, through a translator, etc.)?
iii. Was consent obtained prior to enrollment in the study (i.e., prior to performance of any study related tests and administration of the test article)?
iv. After signing and dating the informed consent document, was each subject or the subject's legally authorized representative given a copy of the consent document?
v. Was the appropriate IRB-approved version of the informed consent document used for all subjects?
vi. If the short form was used (per 21 CFR 50.27(b)(2)), was the informed consent process appropriately documented?
a. Did the subject or the subject's representative sign the short form?
b. Was a witness present, who signed the short form and the copy of the summary?
c. Did the person actually obtaining the consent sign a copy of the summary?
d. Is the case history documented to show whether a copy of the summary and the short form were given to the subject or the subject's representative?
vii. Review the IRB approval letter for the study. Did the IRB stipulate any conditions for the informed

consent process and, if so, did the clinical investigator follow those instructions/stipulations?
b. Review the informed consent documents signed by the subjects. If the number of subjects at the site is relatively small (e.g., 25 or fewer subjects), review 100% of the informed consent documents. For larger studies, a representative number of informed consent documents should be reviewed (for example, may be specified in a sampling plan provided with the assignment).
c. Determine the following:
i. Did the subject or the subject's legally-authorized representative sign the informed consent document prior to entry into the study? If the subject did not sign the informed consent document, determine who signed it and that person's relationship to the subject. Describe how the clinical investigator determined that the person signing the informed consent document was the subject's legally-authorized representative.
ii. Whether subjects signed the version of the informed consent document that was current at their time of entry into the study.
iii. For pediatric studies, was assent obtained from the subjects in addition to the permission of the parents?
iv. Whether the written consent document(s) or oral consent complies with the eight (8) required elements in 21 CFR 50.25(a).

If any problems are found (e.g., investigator failed to obtain consent from one or more subjects, consent was not obtained prior to enrollment in the study, investigator failed to use the correct informed consent document, etc.), the sample should be expanded to determine the extent of the problem. Collect documentation to support each observation. Report the total number of informed consent documents that were reviewed and the number of documents exhibiting the problem.

". In title 21, Code of Federal Regulations (CFR), § 50.3(l), "Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." In 21 CFR 50.3(l), the federal regulations defer to "applicable law". Therefore, who may serve as a legally authorized representative (LAR) is determined by the applicable State or local law.

You might find helpful FDA's guidance document on frequently asked questions. Please see "Institutional Review Boards Frequently Asked Questions - Information Sheet", at www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm and A Guide to Informed Consent Search for FDA Guidance Documents > A Guide to Informed Consent - Information Sheet

Additionally a new *draft* guidance on informed consent was issued in July 2014.
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf

If you would like to report these issues to FDA, please see the link below. The reporting is drug, biologic, and device specific. You can remain anonymous.
Reporting Complaints Related to FDA-Regulated Clinical Trials

I hope this information is useful to you. Please contact us at gcp.questions@fda.hhs.gov if you have further questions.

Kind regards,

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

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: Tuesday, March 24, 2015 7:43 PM
To: OC GCP Questions
Subject: Several questions

I work in a [redacted] department at a hospital that conducts research studies with investigational drugs with patients with dementia. We have a local IRB that follows 45 CFR 46.116 and 21 CFR 50.20 of the federal regulations and our IRB requires a family member or close associate to fill out a consent form along with the patients to agree that they will assist the patient with study compliance. Over the past several months I have been told many puzzling things and witnessed what I consider violation of these regulations. For example:

I have been told by my manager that giving potential subjects the consent forms to take home for review will, "overwhelm" them. It is their policy to give patients a short synopsis of and only present them with the consent at the screening visit (unless they ask for it beforehand) a process which I am told should only take 45 to 60 minutes for the patient (with dementia) to review a 17 to 19 page consent form.

If the subject has a hard time dating and initialing the pages of his consent, I have been instructed that it is permissible to let the caregiver date and initial the pages for them.

My manager said she ignores going over the HIPPA language with patients, because patients know all that information and have seen it before.

My manager said that during the consenting process she only reviews the, "serious adverse events".

I have also been informed by my manager that I give the patients, "too much information" and that I should tell patients and family that joining a study, "is their only hope." We are also encouraged to tell them that, we don't know when the studies will end and that we need to show more, "urgency" when discussing trials with them.

When I expressed my concerns with the institutional review board they explained that my department policy is to not give consent forms to potential subjects because the consent forms are too long and complicated and that the subjects would not benefit from having more time to review them anyway. They did not answer my question why surrogate consent forms are not being used for subjects that have dementia or why subjects are being asked to sign consent forms that are, "too long and complicated".

The IRB director even made an analogy that sometimes doctors have to do things that are questionable (drawing blood from patients in the case of an emergency situation) in order to save a patient's life. It is clear to me, as it should have been to her that a research study is not, "treatment" or a life saving situation, it is a voluntary research study that uses an "experimental" medication that does not propose to, "treat" participants or even promise a benefit to them.

These incidents do not appear to comply with the above federal regulations for consenting subjects or GCP as I understand them. Please provide me with some guidance regarding consenting these subjects and how I am to interpret the rules as they are written.

I did take these issues up with the OHRP, but they said that they do not have authority over my institution as they did not check the box on their FWA.