From: OC GCP Questions
To: [redacted]
Subject: RE: PI access of EMRs to assess AEs for subjects discontinued from IP; PI seeking contact info from friends/family for subjects lost to follow up
Date: Wednesday, August 20, 2014 9:22:00 AM

Dear [Redacted],

Thank you for your questions and for your previous clarification that the investigational product (IP) you refer to is an investigational drug product. I apologize for the delay in response, but as I mentioned to you, I consulted multiple FDA colleagues, and we agree that there is not enough information about the specific sponsor scenario to be able to provide a definitive response. However, my OGCP colleagues and I wanted to share a few thoughts with you that we hope are helpful. I have pasted portions of your e-mail into my response below for your convenience.

Question:

> The relevant study is a multi-center long-term cardiovascular outcomes study of an investigational product. A number of PIs have access to the EMRs [electronic medical records] of affiliated practices for their subjects who have been prematurely discontinued from IP and have stopped attending regular study visits; though have agreed to one final contact at the end of the study. ***Would FDA expect that PIs at these sites query their discontinued subjects' EMRs to obtain AE-related data?*** (the consent provided by subjects would allow for this type of access of medical records)

Response:

In the situation you describe, assuming that (1) the PI has indeed lost contact with the subject, *and* (2) the consent provided by the subjects allows PIs to query discontinued subjects' EMRs, then adverse event information should be collected when available. It's not clear, however, why some PIs have access to the subjects' medical records but others don't.

Information on adverse events is a critical component of case histories in which investigators are required to document all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control (21 CFR 312.62(b)). Additionally, the regulations relating to the submission of marketing applications require the submission of all relevant data in order for FDA to determine whether a product meets the standard for approval. For example, if subjects did not complete the study because of an adverse event, such information is required in a new drug application (21 CFR 314.50(f)(2)). FDA's guidance on Data Retention when Subjects Withdraw from FDA-Regulated Clinical Trials (http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf) describes follow-up after premature discontinuation is acceptable when the situation is discussed in the IRB approved consent form (page 6).

In general, it is consistent with good clinical practice (GCP) for PIs to follow up with discontinued subjects to determine why the individuals dropped out of the study. (See FDA's official guidance, ICH E-6 Good Clinical Practice: Consolidated Guidance, Section 4.3.4: "Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights." Here is a link to the complete text of the guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf).

As you know, there might be any number of reasons why a subject discontinues participation in a study. Some reasons may necessitate the PI to continue to follow up the subject (e.g., the subject had an ongoing SAE at the time of discontinuation, and the PI follows the subject until the SAE is resolved), while others might not (e.g., the subject moved to another city and found continued participation in the study too inconvenient).

That said, the scenario you describe raises additional questions:

- We do not understand why only some PIs will have access to the EMRs of the discontinued subjects (through their affiliation with the medical practices), if the consent form indeed allowed such access. That is, are there other PIs in the same study who would not have continued access to EMRs for discontinued subjects because they don't have such affiliations?

- If only some of the PIs query EMRs for their subjects who have been prematurely discontinued, could this create a disparity in data collection processes across multiple sites?

Did the sponsor consult with the FDA review division about this plan? As suggested in ICH E6, Section 6.8, Good Clinical Practice: Consolidated Guidance, the protocol should include safety assessment information such as:

> 6.8.1 Specification of safety parameters.
>
> 6.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.
>
> 6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
>
> 6.8.4 The type and duration of the follow-up of subjects after adverse events.

We recommend that the protocol and sponsor provide clear information about the "when", "where" and "how" for collection of safety data as well as follow up of any ongoing AEs/SAEs at the time of discontinuation.

Question:

> The consent provided by subjects to date allows PIs to contact discontinued subjects' PCPs to obtain primary outcomes data at the end of the study. The sponsor is drafting a proposed consent amendment whereby subjects would be asked to provide a contact person (e.g. friend or family member) who could help PIs re-establish contact with discontinued subjects lost to follow up during the study. The friend/family would be approached for current contact information (no medical information) for subjects who have been lost to follow up to facilitate ongoing data collection prior to the end of the study. At present, some PIs have contact information for friends/family members of discontinued subjects lost to follow up; the subjects have not provided consent for PIs to approach these individuals to obtain current subject contact information. Our IRB's position is that subject consent would be required before a PI approaches a subject's friend/family to obtain current contact information for a discontinued subject lost to follow up. ***Can FDA comment upon whether it would ever be appropriate for a PI to approach a subject's friend/family to obtain current contact information for a discontinued subject lost to follow up without having the subject's prior consent to do so?***

Response:

It appears that the current IRB-approved consent form (and protocol we assume) permits PIs to contact discontinued subjects' primary care physicians (PCPs) to obtain primary outcomes data at the end of the study only, and the sponsor is drafting a proposed consent amendment whereby subjects would be asked to provide a contact person (e.g. friend or family member) who could help PIs re-establish contact with discontinued subjects who are lost to follow up during the study (we assume this will also be included in an amendment to the protocol). This friend/family contact would be approached by the PI only for current contact information (i.e., no medical information) for subjects who have been lost to follow up to facilitate ongoing data collection prior to the end of the study. You also said that at present, some PIs have contact information for friends/family members of discontinued subjects, however, it is not clear why some PIs have such contact information and others don't. In any event, it sounds like none of the subjects have provided their consent for PIs to approach any friend/family contact on their behalf.

Again, it is difficult to answer this question without any knowledge of the study, particularly what the protocol dictates, or what the amendment will include. However, generally speaking, the subject would have to give their consent to provide a contact person (e.g. friend/family) and then to allow the PI to contact that friend/family member on their behalf.

Again, I apologize for the delay in this response and that I could not be more helpful, but there are too many details about this scenario that would need to be considered to be able to give a more robust response.

We suggest you ask the sponsor for more information and ask them whether or not they contacted their FDA review division about these issues. Follow up questions regarding specific products or trials should be directed to the appropriate FDA review division by the sponsor.

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, July 15, 2014 11:26 AM
To: OC GCP Questions
Subject: PI access of EMRs to assess AEs for subjects discontinued from IP; PI seeking contact info from friends/family for subjects lost to follow up

Good morning,

A study sponsor recently posed two novel issues to our IRB and we are requesting the FDA's guidance.

The relevant study is a multi-center long-term cardiovascular outcomes study of an investigational product. A number of PIs have access to the EMRs of affiliated practices for their subjects who have been prematurely discontinued from IP and have stopped attending regular study visits; though have agreed to one final contact at the end of the study. ***Would FDA expect that PIs at these sites query their discontinued subjects' EMRs to obtain AE-related data?*** (the consent provided by subjects would allow for this type

of access of medical records)

The consent provided by subjects to date allows PIs to contact discontinued subjects' PCPs to obtain primary outcomes data *at the end of the study*. The sponsor is drafting a proposed consent amendment whereby subjects would be asked to provide a contact person (e.g. friend or family member) who could help PIs re-establish contact with discontinued subjects lost to follow up during the study. The friend/family would be approached for current contact information (no medical information) for subjects who have been lost to follow up to facilitate ongoing data collection *prior to the end of the study*. At present, some PIs have contact information for friends/family members of discontinued subjects lost to follow up; the subjects have not provided consent for PIs to approach these individuals to obtain current subject contact information. Our IRB's position is that subject consent would be required before a PI approaches a subject's friend/family to obtain current contact information for a discontinued subject lost to follow up. ***Can FDA comment upon whether it would ever be appropriate for a PI to approach a subject's friend/family to obtain current contact information for a discontinued subject lost to follow up without having the subject's prior consent to do so?***

Thank you for your assistance.

Best regards,

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