From: OC GCP Questions
To: [redacted]
Cc: Cullity, Constance; Parker, Catherine; Walters, Dana L
Subject: RE: Follow-up to my questions
Date: Friday, March 06, 2015 2:57:00 PM

Dear [redacted] -

Thank you for your telephone call and for subsequently sending your questions in written format. OGCP is responding on behalf of FDA, after conferring with OSI.

Your first question specifically asks whether it is a requirement to get prospective IRB approval for a planned deviation in inclusion/exclusion criteria. As we discussed, the FDA's regulations do not define the term "protocol deviation". A protocol deviation, such as a planned deviation to the inclusion/exclusion criteria described in your first question, could be considered a change to the protocol. In general, changes or deviations from the protocol require IRB approval prior to implementation, unless the change is intended to eliminate an apparent immediate hazard to subjects, in which case it may be implemented immediately provided the IRB is subsequently notified in accordance with 21 CFR 56.104(c).

The IND regulations at 21 CFR 312.66 require that the investigator not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. The IDE regulations at 21 CFR 812.150(a)(4) require that the investigator notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval of FDA and the IRB, in accordance with 812.35(a), also is required. The IRB regulations at 21 CFR 56.108(a)(3) and (4) require the IRB to follow written procedures for ensuring prompt reporting to the IRB of changes in research activity, and 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.

FDA's Compliance Program Guidance Manual (CPGM) for Bioresearch Monitoring of Clinical Investigators and Sponsor-Investigators, available at http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf, provides instructions to FDA field personnel on the conduct of an inspection and includes the following guidance for inspections of investigators in relation to adherence to the protocol (See Part III, section D.3.):

> **Verify** that the clinical investigator followed the study protocol approved by the IRB. The investigator is responsible for ensuring that an investigation is conducted according to the investigational plan. (21 CFR 312.60; 812.100)
> **Review** any changes to and deviations from the protocol.
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> **Protocol changes/amendments**. During the course of a study, a protocol may be formally changed by the sponsor. Such a change is usually prospectively planned and implemented in a systematic fashion through a protocol amendment. Protocol amendments must be reviewed and approved by the IRB, prior to implementation, and submitted to FDA.
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> **Protocol deviations**. A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally communicated to FDA. "Protocol deviation" is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations.
> **Determine** whether changes to the protocol were:
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> i. Documented by an amendment, dated, and maintained with the protocol;
> ii. Reported to the sponsor (when initiated by the clinical investigator); and
> iii. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

As we discussed on the telephone, protocol deviations are also mentioned in the ICH GCP E6 Good Clinical Practice: Consolidated

Guidance, (which is recognized as official FDA guidance – see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf). Section 3.3 of this guidance addresses IRB/IEC procedures and includes the following relevant information:

> 3.3 Procedures
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> The IRB/IEC should establish, document in writing, and follow its procedures, which should include:...
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> 3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).
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> 3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:
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> (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see sections 3.3.7, 4.5.2, 4.5.4).
> (b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).
> (c) All adverse drug reactions (ADRs) that are both serious and unexpected.
> (d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

Section 4.5 of the ICH GCP E6 guidance addresses investigator compliance with the protocol and states:

> 4.5 Compliance with Protocol
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> 4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.
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> 4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).
>
> 4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
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> (a) To the IRB/IEC for review and approval/favorable opinion;
> (b) To the sponsor for agreement and, if required;
> (c) To the regulatory authority(ies).

IRBs should prepare and maintain clear written procedures addressing things such as (1) deviations that are considered to be changes in research, and (2) investigator responsibilities for prompt submission of deviations from, or changes to the protocol to the IRB, and (3) IRB review of such changes. It is also important to ensure that the investigator is familiar with the IRB's written procedures/requirements.

For the second scenario you described, and as we discussed on the telephone, FDA doesn't have any insights about this particular issue. The regulations require sponsors to choose qualified investigators so if there are any questions or concerns about the sponsor's decisions or actions, the investigator should contact the sponsor to further discuss.

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: Friday, February 27, 2015 6:03 PM
To: Walters, Dana L
Cc: Donnelly, Janet
Subject: Follow-up to my questions

Dear Dana (and Janet):

As a follow-up to my call yesterday, I am presenting my questions/issues in writing for your/your division's consideration:

1) FDA's view on whether prospective IRB approval of protocol deviations/waivers for one or more subjects is needed. Examples include:
-waiver of an inclusion or exclusion criterion. Normally industry requires sponsor's (usually medical monitor) approval of any planned deviation of the inclusion/exclusion criteria. Some sponsors state that the waiver should also be approved by the IRB prior to proceeding to implement the waiver while others (many?) are silent on the IRB requirement. Many IRBs at prominent academic institutions have implemented clear written policies requiring such. AAHRPP, to my knowledge, promotes such practice. ICH E6 3.7 is interpreted by many in a manner that agrees with this standard. ICH E6 3.8 provides a similar standard with prompt reporting to the IRB to eliminate immediate hazards to subjects, but does not go as far as stating that approval is required. I have seen an FDA audit (within the past six months) cite an investigator for failure to obtain approval from a sponsor and report the deviation to the IRB, but not go as far as stating that the IRB approval should have also been obtained. OHRP has taken the position over the years that prospective IRB approval is required for any change to the protocol, even if for one subject, unless the change is necessary to remove an immediate harm to the subjects.

The issue then can be raised to other deviations. Some deviations would be more obvious as to why prospective IRB approval may be required, such as changes in dosing, monitoring of subjects, etc. Other deviations would appear to be less obvious such as out of office window visits due to holidays, vacations, adverse weather conditions. Since these other areas are more murky, let's focus the question only on the following for now:

Does the Division of Scientific Investigations consider it a requirement to obtain prospective IRB approval of a planned deviation in inclusion/exclusion criteria?

2) I described a situation whereby an investigator who had a FDA warning letter about [Redacted]
has now been removed from the research team (he was listed as a co-investigator) for
a clinical trial by four different sponsors. The odd thing is that all four of these happened in the past two months or so and 2-3 of them may have occurred within a three week period. While I do not expect FDA to be able to do anything about this, I wanted to bring this to your attention to see if you/your colleagues have heard of similar situations and whether there may be any solution. The investigator had since moved to another institution and is now part of a well-run research team. He was a co-investigator under a prominent investigator with a good reputation, when the requests came in from the four sponsors to remove him from the team. I personally have been involved in an audit of the prominent investigator and found that the research records, including the regulatory binder, to be well managed and in compliance with FDA regulations and GCP. The research team includes about [Redacted] individuals and they were truly a well-run operation. The investigator is a PI on NCI studies and has been audited by NCI without any significant findings. He seems to have learned from the FDA warning letter and seems to be committed to conducting research with a high degree of quality. Right now, I plan on approaching the sponsors and trying to find out if they will reconsider. If you hear

of any insights that may help, please let me know.

I also contacted Janet Donnelly in the Office of GCP to gain her and her office's view on the above two items. She may be reaching out to you.

Sincerely,

[redacted]