From: OC GCP Questions
To: [redacted]
Subject: Planned Deviation
Date: Thursday, August 14, 2014 12:07:35 PM

Good afternoon –

We are not familiar with the term “planned deviations”. The protocol should be followed as written. If the subject did not meet inclusion/exclusion criteria for example, even if approved by the sponsor, we would consider this a protocol violation, would be considered non-compliance with the regulations, and would be cited during a FDA inspection. Protocol amendments can be made as the study goes forward if needed. If the sponsor wants to change or amend the protocol, they would need to get approval from FDA and the IRB

FDA's regulations would require notification of the reviewing IRB as an unanticipated problem involving risk to human subjects (see 21 CFR 312.66, 812.150(a)(1) and 56.108(b)). I am unclear if the scenario you describe involves risk to human subjects.

Additionally, FDA would expect an investigator, the investigational site and/or the sponsor to take corrective actions when issues arise during a clinical investigation and to document the actions taken. Several FDA guidance documents indicate this. See for example:

“Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects” (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf) includes as a possible element for an investigator’s plan to supervise and oversee a clinical trial “A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study.”

“IRB Continuing Review after Clinical Investigation Approval” (available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf) indicates that, when an IRB notes a pattern of non-compliance with the requirements for continuing review, “the IRB should determine the reasons for the non-compliance and take appropriate corrective actions.”

Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” draft guidance (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf), when discussing possible components of a monitoring plan to address management of noncompliance, “Processes to ensure that root cause analyses are conducted where important deviations are 456 discovered and that appropriate corrective and preventive actions are implemented to address issues identified by monitoring.”

“FDA Inspections of Clinical Investigators” (available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf) indicates that an FDA investigator may inspect records to ascertain “corrective actions in response to previous FDA inspections, if any”; that if significant violations of FDA regulations are found, a warning letter may be issued and “include a request for correction and a written response to the agency”; and that “If, in response to the NIDPOE (notice of initiation of disqualification proceedings and opportunity to explain), the investigator provides an explanation that is accepted by the agency and the disqualification is not warranted, alternatives such as a detailed corrective action plan may be considered.”

You can report serious non-compliance to FDA using the web page links below. Please include the IND number in your reporting. Also, please note that the reporting is product specific (drugs, biologics, and medical devices). .
Report Problems to FDA > Suspension or Termination of IRB Approval

I suggest discussing the situation you describe with your reviewing IRB.

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
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [redacted]
Sent: Wednesday, August 13, 2014 1:10 PM
To: OC GCP Questions
Subject: Planned Deviation

Dear Sir or Madam,

Often times our IRB learn of exemptions (we refer to them as planned deviations) granted by a sponsor that allows an investigator to enroll a subject who did not meet all inclusion/exclusion criteria. Typically the investigator contacts the sponsor and requests approval to enroll the subject although the subject did not meet criteria X. The sponsor either approves the exemption or does not approve.

In other situations, an investigator may request an exemption to allow a subject to be seen/treated outside of the protocol specific visit window. If the investigator anticipates in advance that the subject will not be able to seen during visit window, they may contact the sponsor and requests approval of this out of window visit. The sponsor either approves the exemption or does not approve.

Our question is, do these exemptions require prior IRB review and approval?

It is our understanding that per 56.108, the IRB shall follow written procedures 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. In FDA's opinion, are either or both of the scenarios mentioned about considered to be 'changes in approved research', which would require not only sponsor approval, but also IRB approval prior to implementation?

We are under the belief that an exemption (planned deviation) to allow a subject to enroll who did not meet all inclusion/exclusion criteria must receive prior IRB approval before the subjects enrolls. However, it appears that not all sponsors are in agreement.

Would a failure to seek prior IRB approval for the enrollment of a subject who did not meet all inclusion/exclusion criteria, but did receive a sponsor exemption, represent non-compliance with the regulations?

Thank you in advance for your reply.
[Redacted]