From: OC GCP Questions
To: [redacted]
Subject: Notification of protocol deviations to FDA
Date: Wednesday, October 22, 2014 2:05:30 PM

Good afternoon –

With regard to protocol deviations, the GCP document ICH E6, which is considered official FDA guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf) , states, under section 4 on the investigator, that deviations from the protocol must be reviewed and approved by the sponsor and reviewing IRB before enactment, except when necessary to ensure the rights, safety, or welfare of study subjects (see section 4.5). Any deviations that occur without such prior approval must be reported to the IRB, the sponsor, and, where applicable, regulatory agencies. Additionally, in the compliance program guidance manual (CPGM) which provides instructions to FDA investigators for conduct of an inspection of a clinical investigator (CI) (http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf), Part III (Inspectional) discusses protocol deviations with regard to inspecting compliance with the protocol in section D and includes a discussion of what FDA considers a protocol deviation.

Deviations from the protocol lessen the poolability of study data across sites and therefore the power of the given study. Therefore, sponsors attempt to write study protocols such that deviations will be as infrequent as possible. In assessing the data submitted to support marketing, FDA therefore needs to have complete data on all protocol deviations that occurred during the study to ensure the sponsor performed a proper analysis of study results.

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 he scenario you describe involves risk to human subjects in your particular study.

If violations (from FDA regulations) were found during an FDA inspection, 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.”

Protocol deviations should be reported to the sponsor and the reviewing IRB. They can assist in determining with the deviations need to be reported to FDA. If unsure, you can always contact the regulatory project manager of the IND at FDA. This person can provide guidance.

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, October 22, 2014 8:03 AM
To: OC GCP Questions
Cc: [redacted]
Subject: Notification of protocol deviations to FDA

Dear Sirs,
[redacted]
is the Sponsor of different clinical studies in USA.

We would appreciate if you could clarify the following:

Protocol deviations could be detected during the conduct of a clinical study (i.e. an analytical parameter has not been performed, the premedication has not been administered correctly, etc.). Should these protocol deviations be notified to FDA?

Many thanks in advance
Best regards
[redacted]