From: OC GCP Questions
To: [redacted]
Subject: Question about protocol deviation
Date: Monday, December 14, 2015 9:48:22 AM

Good morning –

With regard to protocol deviations, the GCP document ICH E6, which is considered official FDA guidance (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) (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. It states --

A protocol deviation 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.

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 does not specifically define major and minor protocol deviations.

You may wish to review the FDA guidance document below related to protecting the welfare of study subjects.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

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
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Office of Good Clinical Practice
Office of the Commissioner, FDA

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: Monday, December 14, 2015 2:17 AM
To: OC GCP Questions
Subject: Question about protocol deviation

Dear Sir/Madam:

I would like to ask about the protocol deviation. Is there any guidance or regulations regarding the definition of protocol deviation and its classifications, eg. major or minor, what are major PDs, and what are minor PDs?

As we defined some major PDs in our plan, and ask for prompt reporting of the PDs, however one site asked for the "official" regulations or guidance to be presented to it.

Best regards
[redacted]