From: OC GCP Questions
Sent: Tuesday, September 16, 2014 11:00 AM
To: [redacted]
Subject: Protocol deviations

Importance: High

Good morning –

Since you are asking about waivers and protocol deviations together, I will assume the waivers are to requirements in the protocol and are granted by the study sponsor. There is very little discussion of protocol deviations in FDA guidance documents and none with regard to waivers that I am aware of.

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.

While I am not aware of any discussion in a guidance document, FDA has addressed protocol waivers in Untitled and Warning Letters following FDA inspections, particularly to sponsors who have been found to give numerous protocol waivers. Since the effect is the same on the poolability of the data as protocol deviations, sponsors should discourage requests for protocol waivers. If many requests are received for a given study, the sponsor needs to reassess the protocol to determine if an amendment is necessary with regard to any requirement CIs find difficult to meet. A meeting with CIs may be necessary to determine if such requirements are too restrictive given the nature of the intended study population or present a major departure from standard medical practice that the CIs do not see as warranted for accruing the desired study endpoints.

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.

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.”

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: Friday, September 12, 2014 3:25 PM
To: OC GCP Questions
Subject: Protocol deviations
Importance: High

I am preparing a presentation for an upcoming industry conference. Included in my presentation I intend to speak about protocol deviations/violations/exceptions/waivers. In my greater than 25 years in the industry, these terms have been utilized; however, I am unable to locate these terms in the federal regulations related to IRBs, protection of human subjects and good clinical practices.

From my perspective, protocol deviations, violations, exceptions and/or waivers should be viewed as non-compliance.

Review of FDA Warning Letters seem to identify these issues as failure to comply.

I would greatly appreciate the FDA’s view at your earliest convenience as my slides are due by September 19, 2014.

Regards,
[redacted]