From: OC GCP Questions
To: [redacted]
Subject: Audits and monitoring plans
Date: Monday, February 23, 2015 12:42:49 PM

Good afternoon –

The two guidance documents below should assist you with understanding FDA's current thinking on the topic. FDA believes that employing a risk-based approach to a clinical study means sponsors should consider what errors would matter when accruing data to support the safety and effectiveness/efficacy of an investigational product. When reviewing the proposed protocol for a study that means conferring with potential clinical investigators to ensure the inclusion/exclusion criteria are adequate and not too restrictive, that proposed follow-up visits and tests are necessary and appropriate, that confounding medications and conditions have been sufficiently considered, that the data needed to support the primary endpoints are appropriately collected, and that unnecessary data will not be collected. It also means anticipating where problems may occur - for example, with accruing subjects, maintaining subject and investigator compliance, accurately recording essential data, and considering upfront what can be done to prevent the problems or at least mitigate their impact. It is what is commonly referred to as building quality into a clinical study from the start. It is similar to the same approach to the manufacture of products in that you consider what can go wrong, the potential impact of problems/errors on the quality and integrity of the end-product (here the data needed to support safety and effectiveness), which potential problems/errors would actually matter, and ways to prevent or handle them should they occur.

Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects" (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf)

Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" draft guidance (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf),

FDA's bioresearch monitoring compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM 7348.810)15 and for CIs and sponsor-investigators (CPGM 7348.811)16 are compatible with the approaches described in the monitoring guidance. For example, CPGM 7348.810 informs FDA field staff that the regulations do not prescribe a specific monitoring technique. While CPGM 7348.810 refers to site visits and does not discuss centralized monitoring, the focus is on the review of monitoring activities through documentation and whether these activities were carried out in accordance with the sponsor's (or CRO's) monitoring procedures.

Please see the link below to FDA's compliance programs.
Clinical Trials and Human Subject Protection > Bioresearch Monitoring Program (BIMO)

I cannot say if a 483 would be warranted. The FDA investigators inspect against the protocol and the monitoring plans should prevent deviations/violations from the protocol. The sponsor's monitoring plan should assure compliance.

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, February 20, 2015 3:38 PM
To: OC GCP Questions
Subject: Audits and monitoring plans

In regard to audits of clinical investigators/ study sites or sponsors conducted by the FDA, does the auditor use the information in a Monitoring Plan (MP) as a guide to the conduct of the study. What role does the MP play in an audit.

For example, if in the MP it states that monitoring visits should be conducted 2 weeks after a first subject is randomized, and in fact the visit did not occur until 4 weeks after the 1st subject was randomized, would this result in a Form 483 being issued to the sponsor? Or, if for instance the MP states that the monitoring visits should be every 4-6 weeks and due to low enrolment the visits are 8-10 weeks apart would this result in a 483 to be issued?

Thanks, I appreciate your consideration of this question.

Cheers,
[redacted]