From: OC GCP Questions
To: [redacted]
Subject: Extra Assessments on visits as Protocol Deviation/Violation
Date: Tuesday, March 24, 2015 11:01:50 AM

Good morning –

From a FDA perspective, it is difficult for me to specifically answer your question as I am unclear what you mean by "extra assessments". I can provide the following general information on protocol deviations and violations.

The IND regulations at 21 CFR 312.66 require that the investigator not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. The IDE regulations at 21 CFR 812.150(a)(4) require that the investigator notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval of FDA and the IRB, in accordance with 812.35(a), also is required. The IRB regulations at 21 CFR 56.108(a)(3) and (4) require the IRB to follow written procedures for ensuring prompt reporting to the IRB of changes in research activity, and 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.

FDA's Compliance Program Guidance Manual (CPGM) for Bioresearch Monitoring of Clinical Investigators and Sponsor-Investigators, available at http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf, provides instructions to FDA field personnel on the conduct of an inspection and includes the following guidance for inspections of investigators in relation to adherence to the protocol (See Part III, section D.3.):

Verify that the clinical investigator followed the study protocol approved by the IRB. The investigator is responsible for ensuring that an investigation is conducted according to the investigational plan. (21 CFR 312.60; 812.100) Review any changes to and deviations from the protocol.

Protocol changes/amendments. During the course of a study, a protocol may be formally changed by the sponsor. Such a change is usually prospectively planned and implemented in a systematic fashion through a protocol amendment. Protocol amendments must be reviewed and approved by the IRB, prior to implementation, and submitted to FDA.

Protocol deviations. A protocol deviation/violation 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. Determine whether changes to the protocol were:

i. Documented by an amendment, dated, and maintained with the protocol;
ii. Reported to the sponsor (when initiated by the clinical investigator); and
iii. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

Protocol deviations are also mentioned in the ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance – see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf). Section 3.3 of this guidance addresses IRB/IEC procedures and includes the following relevant information:

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:...

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see sections 3.3.7, 4.5.2, 4.5.4).
(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).
(c) All adverse drug reactions (ADRs) that are both serious and unexpected.
(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

Section 4.5 of the ICH GCP E6 guidance addresses investigator compliance with the protocol and states:

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

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

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is 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: Tuesday, March 24, 2015 6:52 AM
To: OC GCP Questions
Subject: Extra Assessments on visits as Protocol Deviation/Violation

Dear Sir or Madame,

Is it correct that FDA has no the separate guide for Protocol Deviations/Violations?

Based on FDA's judgement – can extra assessments (which is not expected by Schedule in Protocol and done during subject's visit at site in frames of Protocol) can be considered as Protocol Deviation/Violation?

Thank you very much in advance.

Sincerely,

[redacted]