From: OC GCP Questions
To: [redacted]
Subject: Additional I/E Requirements - Not Specified by Protocol
Date: Thursday, August 06, 2015 7:25:40 AM

Good morning –

I assume when you state “volunteers” you mean study subjects. Also I am unclear what you mean by “restrictions”. From an FDA perspective, the protocol should be followed as written. 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).

I hope this information is helpful. Please contact us again at gcp.questions@hhs.gov should you have any questions.

Kind regards,

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Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [redacted]
Sent: Wednesday, August 05, 2015 2:59 PM
To: OC GCP Questions
Subject: Additional I/E Requirements - Not Specified by Protocol

Hello,
During the recruitment and screening process, investigators and the members of the clinical team are placing additional restrictions on the volunteers that are not required by the protocol or documented in a local SOP. My understanding is that the protocol is the primary source of I/E and if the protocol is silent, additions would need to be supported by a local SOP. Could you clarify if this is this also the expectation of the FDA and that no additional restrictions should be required of volunteers without procedural documentation? Are there any repercussions should this be discovered during an inspection? Thank you in advance.

Kind regards,
[redacted]