From: OC GCP Questions
To: [redacted]
Subject: Qs on subject discontinuation from the study
Date: Thursday, January 04, 2018 12:37:00 PM
Attachments: [redacted]

Good afternoon –

The protocol should be followed as written. I cannot specifically answer your question as I don't know the specifics of the study. It is probably best to have the sponsor contact the FDA regulatory project manager of the IND to advice.
I can however offer you the following information.

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 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).

For device studies: determine whether deviations to the protocol were:

i. Documented, showing dates of and reason for each deviation;

ii. Documented, with prior approval from the sponsor for deviations from the investigational plan, except if emergency use (see iv).

iii. Documented, with prior approval from the reviewing IRB and FDA for deviations from the investigational plan that may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, except if an emergency (see iv).

iv. If emergency use, documented notification of 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 addition, determine that this notice was given within 5 working days after the emergency occurred. (21 CFR 812.150(a)(4))

Collect correspondence or other documentation that supports adverse inspectional observations.

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: Wednesday, January 03, 2018 6:39 AM
To: OC GCP Questions <gcp.questions@fda.hhs.gov>
Subject: Qs on subject discontinuation from the study

Dear FDA,

I have a Question on subject discontinuation from the study.

Per protocol, Hypertension grade 4 is one of the study discontinuation criteria.
Patient had hospitalized due to grade 4 HP but at that time investigator did not discontinue the subject by error but 6 weeks after this issue was reported to the sponsor.
When this issue was reported 6 weeks later, subject's condition was improved and no safety concern by the investigator, and investigator insisted to continue the subject in the study since there was no safety concern and study drug benefits for the subject.

In this case, can sponsor requests the investigator to discontinue that subject from the study as per Protocol or
can investigator continue the subject but report the issue as protocol deviation?

Many thanks

[redacted]