From: OC GCP Questions
To: [redacted]
Bcc: Wolanski, Nicole
Subject: RE: Question of protocol deviations and acceptable tracking means
Date: Friday, May 12, 2017 3:42:00 PM

[redacted],

Thank you for your question. The answers to some questions we receive depend greatly upon the circumstances of a specific study. It is often difficult to provide specific responses to general questions, such as in the scenario you describe, because not all of the details are included.

The regulations do not define "protocol deviation". When the regulations are silent, IRBs, institutions, sponsors, investigators are free to develop their own procedures and practices as long as applicable regulatory requirements are met.

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).

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.

You state that the CRO and investigator have different interpretations on this matter. I recommend that you additionally consult with the sponsor and IRB to discuss if the situation you asked about would be considered a protocol deviation as the details in the IRB-approved protocol will be important to consider in making this determination.

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

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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: Friday, May 12, 2017 4:10 AM
To: OC GCP Questions
Subject: Question of protocol deviations and acceptable tracking means

Dear US FDA,

This email is about FDA's expectation on tracking protocol deviations (PD). For the examples below:

Should protocol deviation be recorded into PD log for each of the following cases (phase I PK study)?

1. Randomized subject withdrew consent just prior to dosing
2. Randomized Subject who did not withdraw consent, but did not get dosed due to technical issue in inserting cannulation for IV drug administration. Investigator withdrew the subject due to unable to administer dose.
3. Randomized, dosed subjects who withdrew consent in mid-study and not complete all follow up visits and PK timepoints intended by protocol design.

By CRO project team interpretation, these cases are to be recorded as protocol deviations as they did not follow intended protocol design and procedures, despite all parties handled these in GCP-compliant manner. These would be important information to rest of study team, as basis for determining which subjects should be included or excluded into various safety and PK analysis set. The protocol deviation log seem appropriate place to document and communicate these info consistently.

By the investigator's interpretation, site does not think these should be recorded as protocol deviations because they followed GCP in handling the withdrawal requests or technical issue leading to withdrawal, and any protocol would have to allow subject to withdraw at any time.

Would FDA expect site to track points 1-3 as deviation in site file?
Would FDA expect tracking point 1-3 as deviations for the CRO/sponsor file?

Side question: if FDA does not consider these should be tracked into protocol deviation log, then what is FDA's acceptable means for tracking and presenting such info? (eg. Only use real-time eCRF data listing during active study is fine? For archived study when eCRF is no longer available, what tracking is acceptable to FDA during an inspection?)

Regards,

[redacted]