Probably the most feared study-related problems that principal investigators (PIs) and research coordinators share feelings of dread over are protocol deviations and (even worse) protocol violations.

There is a great deal of chatting online about these issues to go along with the animated discussions that arise in any PI office when clinical research associates or auditors come to “visit,” hopefully not “for cause,” be the event driven by a sponsor, contract research organization (CRO), or the Food and Drug Administration (FDA).

Nonetheless, any site that has completed a study and has zero protocol deviations is either the best site ever created, or perhaps the monitors never noted any problems, but should have.

For example, we just endured the Hurricane Sandy disaster, and perhaps at least 20% of all our randomized patients were “out of window” for their treatments, as there was no power at their home and our site was on generator backup power.

Are these out of window issues defined as protocol deviations or violations? It depends on whom you ask.

Who Says What and Why

My operations manager makes it abundantly clear to our staff that “there are no deviations, only violations.” Yet, we have sponsors who have generated protocol deviation forms for the kind of situation we experienced due to the storm. Some sponsors will approve such deviations from the protocol and call them “minor protocol deviations.”

Let’s look at what the FDA has said about these terms. The following is adapted from the website of First Clinical Research LLC (http://firstclinical.com/fda-gcp/?show=RE+Protocol+violations+versus+deviations&search=word&):

“Protocol violation” does not appear anywhere in FDA’s regulations nor does it appear in the [International Conference on Harmonization] E-6 guidance. I think for the purposes of informing your investigators, you should advise them that any unplanned excursions from the protocol can be referred to as protocol deviations or violations. For example, 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) or unintended instance(s) of protocol noncompliance.

FDA would expect the following with respect to each:

1. The sponsor’s authorization/agreement to prospective exception should be docu-
In Search of a Vanishing Spell

So, now that we have FDA references in hand, let’s go to two recent examples in my research practice, in fact from two days in row, which made us all pause to decide if a deviation or violation occurred and, if so, how serious it was.

A patient was screened for a study that had an inclusion criterion of ages 55 to 80, inclusive. During the 42-day screening period, a host of tests were completed, including MRI, PET scan of the brain, numerous psychometric tests, blood tests, ECG, etc.

Shortly before the day this patient was to be dosed, my research coordinator noted his correct age was 54 years and 4 months. Clearly, he was not eligible to be dosed; or could he be dosed and a “waiver,” or “protocol deviation approval,” be issued? Or would a subsequent protocol amendment be approved to permit this age of 54, or perhaps ages 50 to 80, inclusive, as a way to make this apparent violation/deviation “vanish”?

In such cases, the “practically invisible” PI would simply dose the patient and wait for the monitor to uncover the age issue and deal with it then. Instead of following this course, I contacted the CRO’s medical monitor as well as the sponsor’s medical monitor.

They both felt it would be acceptable, having had the patient complete 100% of the study requirements to be dosed.

I felt participation in the study posed no extra risk to this patient, nor would it harm the integrity of the data, so I too agreed to dose the patient. An e-mail from the CRO summarizing the sponsor’s approval to dose this patient was received, printed, and placed in the files to document this process.

Is this a protocol violation or deviation? The sponsor felt it was a deviation, as it did not affect in anyway the safety of the patient nor the integrity of the data.

The regulatory department of the sponsor, when asked, felt the patient indeed represented a protocol violation and should be dropped and not dosed, based upon the above definition of protocol deviation (not adhering to the

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<th>Protocol Deviation and Protocol Violation Definitions</th>
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| **Protocol Deviation:** An accidental or unintentional change to, or noncompliance with, the research protocol that does not increase risk or decrease benefit; or does not have a significant effect on the subject’s rights, safety, or welfare, and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff. A deviation may be due to the research subject’s nonadherence; or an unintentional change to, or noncompliance with, the research protocol on the part of a researcher. Examples of a deviation include:
- A rescheduled study visit
- Failure to collect an ancillary self-report questionnaire
- Subject’s refusal to complete scheduled research activities

| **Protocol Violation:** Accidental or unintentional change to, or noncompliance with, the IRB-approved protocol without prior sponsor and IRB approval. Violations generally increase risk or decrease benefit, and affect the subject’s rights, safety, or welfare, or the integrity of the data. Examples of protocol violations include:
- Failure to obtain valid informed consent (e.g., obtained informed consent on a non-date stamped form)
- Loss of laptop computer that contained identifiable, private information about subjects
- Accidental distribution of incorrect study medication
- Not following the inclusion/exclusion criteria

Source: https://mmcri.org/deptPages/hrpp/downloads/defineprotocoldeviation.pdf |
inclusion/exclusion criteria). However, it appears that the medical monitor has convinced the regulatory department that this was a case of a protocol deviation.

I felt the same way, and comfortably kept the patient in the trial. The IRB will be notified, if it is in the scope of what is “reportable” to this IRB (each IRB has its own reporting requirements for deviations and violations).

None Shall Pass

The second episode was even more perplexing to the sponsor/CRO/IRB/PI (yours truly) and our operations manager.

The day before this subject was to be dosed (an Alzheimer’s disease patient), it was noted by the CRO’s monitor that the subject had failed to complete a battery of cognitive tests administered via a computer screen.

The patient was unable to clearly understand the test instructions, and just could not complete the test. As such, she was unable to comply with the study instructions, which meant she satisfied one of the nearly 45 exclusion criteria in the protocol, which stated, “inability to comply with study-related testing.”

I looked at the protocol’s primary, secondary, and exploratory outcomes, and none was related to cognitive results, but rather dealt with biological markers that were being measured by various means, along with safety testing of blood, ECG, and urine.

I argued the point that dosing was appropriate in this case, since the patient completed all the other study-related testing and the computerized battery was not a primary, secondary, nor exploratory outcome. In addition, she had satisfied every one of the nearly 35 inclusion criteria and had no other exclusion criteria. In response, the sponsor sent an e-mail approving dosing.

Is this a protocol deviation and, if so, is it a “minor” or “major” deviation; or is it a protocol violation of either a “minor” or “major” severity?

So “No” Really Means “Maybe”?

I don’t think even a seasoned FDA auditor would comfortabably answer these real-world cases in terms of black or white, but would find shades of gray, despite the stern warnings we so often receive from sponsors and CROs at investigator meetings: “No Waivers Will be Granted.”

It all goes to show us how challenging indeed it is to know what is a deviation or violation.