

Bringing Method to the Madness: Protocol Deviation & Violation Codes

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Protocol deviations cause a lot of confusion during clinical studies. This article attempts to answer the basic questions: What is a protocol deviation? What is a protocol violation? Who decides which is which? Who reports them to whom? When? How? Why? What are the problems with the current system? How can we improve it?

Regulatory Requirements

The Code of Federal Regulations very clearly requires that clinical investigators must report study changes and problems to their IRB:

- "Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain....a commitment by the investigator that he or she (a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects." [21 CFR 312.53]
- "An investigator is responsible for ensuring that an investigation is conducted according to...the investigational plan...." [21 CFR 312.60]
- "The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. [21 CFR 312.66]
- "IRB shall....ensur[e] that changes in approved research....may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects." [21 CFR 56.108(a)]
- "IRB shall....follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of... any unanticipated problems involving risks to human subjects or others...[or] any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB." [21 CFR 56.108(b)]
- "Assurances applicable to federally supported or conducted research shall at a minimum include....written procedures for ensuring prompt reporting to the IRB....[of] any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB. [45 CFR 46.103(b)(5)]

The industry has interpreted the above regulations to require investigators to report "protocol violations" to the IRB and sponsor. Although some IRBs require investigators to also report protocol deviations, they are normally just recorded in study documents for sponsor review.

Definitions

Unfortunately, the Code of Federal Regulations (CFR), Form FDA-1572, FDA guidances, and International Conference on Harmonisation (ICH) guidelines do not define the terms "protocol deviation" or "protocol violation." In fact, they do not use the terms, with the following few exceptions:

- CFR 812.140(a) requires that "a participating investigator shall maintain....accurate, complete, and current records relating to...the dates of and reasons for each deviation from the protocol" for Investigational Device Exemption (IDE) but not drug studies.
- The FDA Center for Devices and Radiological Health (CDRH) requires that sponsor progress reports to the FDA include a "description of any deviations from the investigational plan by investigators."
[<http://www.fda.gov/cdrh/devadvice/ide/reports.shtml>, accessed July 31, 2005]
- ICH 4.5.2 says that "investigators should not implement any deviation from....the protocol without agreement by the sponsor and prior review and documented approval....from the IRB/IEC, except where necessary to eliminate an immediate hazard (s) to trial subjects...."
- ICH 4.5.3 says that "the investigator....should document and explain any deviation from the approved protocol." (Note the use of the word "should" instead of "must.")
- ICH 5.18.4 says that site monitor responsibilities include "communicating deviations from the protocol, SOPs [Standard Operating Procedures], GCP [Good Clinical Practice], and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations."
- ICH 5.18.6 says that monitoring reports "should include....the significant.... deviations and deficiencies."
- ICH 8.3.11 requires that the Essential Documents include documentation of "any agreements or significant discussions regarding...protocol violations."
- ICH 3.3 and 4.5.4 use the term "deviation" to refer to changes intentionally made to protect subject safety.

The FDA's usage of the terms "deviation" and "violation" is probably best understood from its Compliance Program Guidance Manual for Bioresearch Monitoring – Clinical Investigators (7348.811):

"....deviations from the regulations that might affect data validity, [or] endanger test subject health or welfare..."

"Issue a Form FDA 483....when deviations from regulations are observed. Deviations from guidance documents do not warrant inclusion on the FDA 483, however, they should be discussed with [site] management and documented in the EIR."

"Deviations from Protocol are not changes in the Protocol."

"....significant violations of the FD&C Act [Federal Food, Drug, and Cosmetic Act] or other Federal statutes..."

In other words:

- "Deviations" are IRB-unapproved departures from the protocol, regulations and guidance documents. One type of deviations are those that might affect data validity or endanger a subject.

- “Changes” in the protocol are pre-approved by the IRB.
- “Violations” are acts that do not comply with Federal statutes (laws).

Although not supported by Federal statutes, regulations, guidance documents, or internal documents, the industry has created the concept of a “protocol violation.” In the absence of official definitions, the industry generally agrees that a protocol deviation is a small violation and a protocol violation is a big deviation. From there, however, definitions quickly diverge and provide only general guidance for classifying many non-compliance events.

Here are plausible definitions of the two terms:

Protocol Deviation. A protocol deviation occurs when, without significant consequences, the activities on a study diverge from the IRB-approved protocol, e.g., missing a visit window because the subject is traveling. Not as serious as a protocol violation.

Protocol Violation. A divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the ICF inaccurate, or (c) impacts a subject’s safety, rights or welfare. Examples of protocol violations may include:

- Inadequate or delinquent informed consent
- Inclusion/exclusion criteria not met
- Unreported SAEs
- Improper breaking of the blind
- Use of prohibited medication
- Incorrect or missing tests
- Mishandled samples
- Multiple visits missed or outside permissible windows
- Materially inadequate record-keeping
- Intentional deviation from protocol, GCP or regulations by study personnel
- Subject repeated non-compliance with study requirements

Interpreting these definitions for a specific event requires a detailed understanding of the causes and circumstances of the event. For example, if a subject did not take his/her study drug in the required time window, is it a protocol violation, a deviation, or perhaps just the subject of a progress note? The classification depends on numerous factors, such as:

- How far out of window did the subject take the study drug?
- Did taking the study drug out of window endanger the subject?
- Did he/she take it with the previous or next dose, creating a risk of overdose?
- Did taking the study drug out of window compromise the data?
- What caused the subject to take the study drug out of window? Did the sponsor ship the drug late? Did the subject just forget? Did the investigator instruct the subject to take the study drug out of window to protect the subject’s safety, for example, if he/she just took the previous dose?

Investigators ask different questions, interpret the answers differently, and classify events differently. IRBs and sponsors may not agree with the classifications. As a result, IRB compliance with its regulatory requirements is inconsistent, sites do not consistently meet their sponsor reporting requirements, and a lot of time is wasted sorting out the confusion.

PDV Codes

The only practical way to obtain consistent reporting is to be very specific about the definitions. Protocol Deviation & Violation (PDV) codes specify 125 different events in 15 categories:

- Informed Consent
- Enrollment
- Tests
- Assessments
- Exams
- Procedures
- Specimens
- Data Collection
- Visits & Telephone Calls
- Documentation
- Study Drug
- Diaries
- IVRS
- Subject Non-compliance
- Adverse Events

Seven optional Causation Codes can be used for further classification.

Table 2 presents the seven PDV codes for data collection, with each type of event classified as a violation, deviation and/or progress note. As illustrated above, classification of a specific event may depend on the circumstances and ramifications, which can be spelled out in the instructions.

Table 2: Data Collection PDV Codes and Plausible Classifications

Code	Description	Violation	Deviation	Note
P1701	Data collection incorrect	X	X	
P1702	Data collection not attempted	X	X	X
P1703	Data collection unsuccessful			X
P1704	Data collection prior to window	X	X	
P1705	Data collection after window	X	X	
P1706	Data collection data lost			X
P1707	Data incorrectly transcribed from source document to CRF			X

It would be helpful for the industry—and the FDA and ICH—to agree on classifications, but PDV codes may legitimately vary by IRB, sponsor and study. What is essential, however, is that the site be provided with the classifications for each study, so it can report noncompliance events according to IRB and sponsor preferences.

Reporting is useful, but what is more important is how the reported information is used. With PDV codes, IRBs, sponsors and sites can identify trouble spots and detect trends. With

that information, they can manage down the number of noncompliance events with targeted interventions, training programs and incentives. They can modify study forms and perhaps even the protocol. When the next study comes around, they will be on the alert for specific problems that cause high rates of noncompliance. In fact, it sounds a lot like a program of continuous improvement.

PDV codes are available at no charge at <http://www.firstclinical.com/resources/codes.html>, along with three other coding systems for clinical research.

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