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Good Clinical Practice Q&A: Focus on SOPs

4.37 Q. What are the FDA's requirements for and expectations regarding standard operating procedures (SOP) for clinical monitors, clinical trial sites, and others involved in clinical trials?

Interestingly, the FDA's drug regulations include SOP requirements only for IRBs. 21 CFR 56.108 requires IRBs "to follow written procedures," and 21 CFR 56.115(a)(b) requires that these written procedures be retained.

FDA regulations include no specific references to, or requirements for, SOPs for sponsors or clinical investigators. For clinical investigators, in fact, there are no references to SOPs in FDA regulations, site inspectional guidances, or the ICH GCP guidance. The regulations do state, however, that the investigator will ensure that all [staff] are informed about their obligations (21 CFR 312.53), and having SOPs is one of the best ways to ensure compliance with this regulation. It is important to note, however, that FDA compliance-related documents establish a clear agency expectation that sponsors will maintain and follow documented SOPs. And, as an agency official recently noted in informal correspondence regarding sponsor SOPs, "FDA, of course, expects SOPs to be followed."

Perhaps the clearest references to the FDA's expectations regarding SOPs for drug sponsors appear in the agency's Compliance Program Guidance Manual (CPGM) 7348.810, which the agency updated in March 2011 and which provides instructions to FDA field inspectors in conducting compliance inspections of sponsors/monitors and clinical research organizations. Specifically, the document makes references to sponsor SOPs in several areas, including monitoring procedures, data collection and handling procedures, quality assurance auditing/quality assurance unit operations, and electronic trials.

It is interesting to note that, although CPGM 7348.810 makes reference to a sponsor's SOPs for monitoring procedures and activities, it also allows for the circumstance in which there are no SOPs. In its instructions to FDA field inspectors, CPG 7348.810 states:

- "Review the procedures, frequency, scope and process the sponsor/CRO/monitor uses to monitor the progress of the clinical investigations. (Device regulations (21 CFR 812.25(e)) require written monitoring procedures as part of the investigational plan.)"
- "Obtain a copy of the sponsor's/CRO's/monitor's written procedures (SOPs and guidelines) for monitoring, and determine if the procedures were followed for the selected study. In the absence of written procedures, conduct interviews of the monitors as feasible and/or otherwise determine how monitoring was conducted."
- "Obtain a copy of any written procedures (SOPs and guidelines) for QA audits and the operation of any QAU."
- "Review the sponsor's written procedures (SOPs and guidelines) to assure the integrity of safety and efficacy data collected from clinical investigators (domestic and international)."
- "Determine how the sponsor/CRO determines which [electronic] records are used for regulatory purposes (e.g., if there is an SOP and if it is followed)."
- "Obtain a copy of any written procedures (SOPs and guidelines) for data verification."

- "Determine if the sponsor/CRO has SOPs for complying with the requirements associated with ClinicalTrials.gov. If so, determine if they complied with these SOPs."

Although it is assumed that sponsors will be cited if they do not follow established SOPs in these areas, it is interesting to note that CGP 7348.810 specifically instructs agency investigators to document deviations only regarding SOPs for data collection and handling procedures: "1. Review the sponsor's written procedures (SOPs and guidelines) to assure the integrity of safety and efficacy data collected from clinical investigators (domestic and international). 2. Verify that the procedures were followed and document any deviations."

As noted, the ICH GCP guidance makes several references to sponsor SOPs, which it defines as "detailed, written instructions to achieve uniformity of the performance of a specific function." Specifically, the ICH GCP guidance states the following:

- "The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)."
- The sponsor should maintain SOPs for using electronic trial data handling and/or remote electronic trial data systems.
- Monitors should follow and be thoroughly familiar with the sponsor's "established written" SOPs, and should communicate SOP deviations to the investigator.
- The purpose of a sponsor's internal audit of a trial, which is separate from routine monitoring or quality control functions, "should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP and the applicable regulatory requirements." "Noncompliance with the protocol, SOPs, GCP and/or applicable regulatory requirement(s) by an investigator/ institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance."

Source

"Good Clinical Practice: A Question & Answer Reference Guide", Barnett International, 2012, #3.33. The Guide is available at http://www.barnettinternational.com in electronic and paper form.