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What's New in GCP?
FDA Officials Detail Risk-Based Trial Monitoring

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Careful, up-front risk assessment is a key to developing a risk-based approach to trial monitoring, FDA officials said in discussing the agency's draft guidance that encourages alternatives to comprehensive on-site monitoring.

"We have heard some concerns from industry that FDA may take regulatory action against a sponsor if they do not perform frequent, on-site monitoring visits and review 100% of the data," Stephanie Shapley, with the FDA Center for Drug Evaluation and Research's Office of Medical Policy, said during an Oct. 24 FDA webinar on the draft guidance.

"This guidance is intended to clearly articulate our recognition of the value of alternative approaches to facilitate change in industry's monitoring practices," Shapley said.

Ann Meeker-O'Connell, acting associate director for risk science, intelligence and prioritization in CDER's Office of Scientific Investigations, said the keys to developing a risk-based approach to trial monitoring were conducting a risk assessment to identify and evaluate risks to critical study data and processes, and designing a monitoring plan tailored to address important and likely risks identified during risk assessment.

Think About What Could Go Wrong

"The concept of risk assessment starts with thinking about what are the things that are likely to go wrong with a trial," Meeker-O'Connell said. "You can't carry on a risk assessment until you have identified the priorities."

The risk assessment should identify the critical data and processes for the trial, such as endpoints, serious adverse events, randomization and blinding, informed consent, and eligibility criteria. "It may be something that is unique to a given trial design or more general things," she added.

The risk assessment considers what could go wrong in collecting critical data or performing critical processes, what the effect would be, and how sponsors and investigators could detect the problem.

This "will allow sponsors to develop a monitoring plan that is tailored to making sure that critical data and critical processes have integrity," she said.

Meeker-O'Connell noted that monitoring is a component of quality risk management and cited an International Organization for Standardization approach to risk management, which is a continual process of planning, doing, checking and acting, with each element feeding into the next.

The Plan – Do – Check – Act (PDCA) cycle is:

> **Plan.** Establish objectives and make plans (analyze the organization's situation, establish overall objectives, set interim targets, and develop plans to achieve them).
>
> **Do.** Implement the plans.

Check. Measure/monitor how the actual achievements meet the planned objectives.

Act. Correct and improve plans and implementation (correct and learn from mistakes to improve the plans).

Protocol Design is Most Important

Although monitoring is an important tool for maintaining trial quality and integrity, as well as the safety of trial participants, Meeker-O'Connell noted, "the draft guidance suggests that the most important tool for ensuring the protection of subjects and for ensuring the integrity of the data is actually a well-articulated and designed protocol."

The same process of risk assessment should be used for developing the protocol by prospectively identifying the important risks to subject safety and data reliability, and then tailoring and conducting the protocol to eliminate or mitigate the risks.

"There are times when you can have a systemic error introduced by trial design that, no matter how intensive a monitoring program is put in place, it may still persist and render the trial unviable," Meeker-O'Connell said.

Chrissy Cochran, with CDER's Office of Compliance, noted that "some data and processes may need more intensive monitoring" because those are the data and processes "that need to be right for your application to be approved." Those include: critical study endpoints, protocol-required safety assessments, subject withdrawals, eligibility criteria, study blind, informed consent, and test article administration and accountability.

"Monitoring is not a one-size-fits-all approach," Cochran reiterated. "It has to be tailored for your specific study."

In developing a monitoring plan, Cochran said the components to consider include:

- descriptions of the monitoring approaches, such as timing, intensity, activities and documentation;
- communication of monitoring results;
- management of non-compliance, training and study-specific information; and
- monitoring plan amendments.

The monitoring plan also needs to discuss what will trigger additional on-site monitoring. Cochran said the type, frequency and intensity of monitoring also depends on the complexity of the study design, the types of endpoints, the clinical complexity of the subjects, investigator experience, relative safety of the product, quantity of the data, and the stage of the study.

How Will Problems Be Handled?

Another key question for the monitoring plan is how non-compliance will be managed. "We know there are going to be issues that are found during the course of the study," Cochran said. "How are you going to ensure that corrective and preventive action plans are being put in place? How are those plans going to be carried out, and how are you going to monitor those plans to ensure follow-through?"

She noted monitoring plans are "fluid documents… I would highly recommend that any time you amend your protocol you also take a look at your monitoring."

And whatever type of monitoring is used, it must be documented, Cochran said. The documentation should include:

- who conducted the monitoring and the date;

- the data and activities reviewed;
- a description of non-compliance, data irregularities, or other deficiencies; and
- the actions taken or recommended.

“Quality is not just about going to the sites and monitoring them or looking at the data centrally,” Cochran said, “it is also ensuring you are communicating with your investigators and training them or retraining them if necessary.

“If you see a particular item over and over,” she added, “maybe that is something that you need to think about adjusting in your protocol or talking about with your investigators to ensure that they are being trained, that they understand what is going on in the protocol, and what it is that they need to do.”

To Find Out More

A video of the webinar is available at https://collaboration.fda.gov/p78245811/.

The draft guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

Information on ISO’s approach to risk management is available at http://www.iso.org/iso/catalogue/management_standards/understand_the_basics.html.

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