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What's New in GCP?
CDER Moves to Risk-based Trial Inspections

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The Center for Drug Evaluation and Research (CDER) is moving to a risk-based approach for bioresearch monitoring (BIMO) inspections. Leslie Ball, head of CDER's Division of Scientific Investigations, said the BIMO program is moving to an "integrated quality risk management approach," which is "a better way to do inspection and enforcement."

Ball said CDER will use an inspection risk model "to more efficiently and effectively select sites for inspection." The model will predict how inspectional findings from a few sites translate across the entire trial and develop a learning algorithm so that risk attributes and weights will evolve over time with a greater understanding of risk.

Ball noted that several sponsors already use such quality risk management systems for trial monitoring and quality assurance auditing.

She said the CDER model for inspection site selection has three levels of risk attributes:

- application level;
- study level, which includes pivotal status, trial design type, and geographical location; and
- clinical site level, which includes enrollment, site specific efficacy, protocol violations, adverse events, serious adverse events, subject discontinuations, financial disclosures and other factors.

Risk Attributes are Used to Rank Sites

Using the risk attributes, the model ranks the sites for possible inspection. The model "looks for data anomalies and allows us to easily pick out the outliers," Ball said.

Traditionally, CDER has assessed trial and data integrity in site inspections at the time of the new drug application submission, with the assumption that the absence of regulatory violations means reliable data and "lots of regulatory violations" means unreliable data.

CDER typically inspected four or five sites per application. If significant violations were identified at one or two sites, the data was deemed unreliable and the FDA conducted a sensitivity analysis that excluded those sites from the efficacy analysis. "The assumption was that the data at all the other sites were reliable."

But the problem is that if a study has 200 trial sites and two of four inspected sites have significant violations, does that mean there are data concerns "at one percent of the sites or that half of the data are not reliable?" What CDER has done is conduct more inspections, which take time and money and cause delays in considering the product for approval.

> "Inspections alone cannot ensure high quality data and protection of subjects; quality should be built into the process."
> — Leslie Ball, head of CDER's Division of Scientific Investigations

Ball cited a case in which one BIMO inspection of four sites found "significant violations affecting data integrity, including retrospective alternation of efficacy data, and loss or discarding of critical source documents." In addition, an inspection of the clinical research

organization (CRO) involved in the study found "insufficient monitoring and insufficient follow up and correction of violations." The agency conducted seven more inspections and the sponsor audited 31 sites (24 percent of the total), including five of the sites CDER inspected. Six of the sites were selected for FDA inspection based on large enrollment and efficacy data favoring the investigational product. One foreign site also was selected.

The additional inspections found that the data were generally reliable, the monitoring was adequate, and the inspections were consistent with the sponsor audits that found "no systematic pattern or incidence of good clinical practice violations that could affect reporting of safety and efficacy data."

"Can't Inspect-in Quality"

One of the key problems has been that the inspections generally take place after the trials are completed and "you can't inspect-in quality," Ball said. "Inspections alone cannot ensure high-quality data and protection of subjects; quality should be built into the process."

This has led to the shift in CDER's approach to assessing data integrity, with a move to a quality systems/quality risk management approach to monitoring and inspecting clinical trials by sponsors and regulators.

The four keys to the new approach are:

- quality by design,
- detect and correct problems in as close to real time as possible, while the study is being conducted,
- focus on key parameters of risk to trial integrity and data quality as well as subject safety and protection monitoring and in selecting sites for inspection, and
- prioritize limited resources.

To build integrity and quality into clinical trials, the sponsor risk management process in developing the trial should consider the:

- Investigational plan, including the rationale for the protocol design and statistical analysis plan
- Governance of the trial, including the role of the data monitoring committee, the trial management committee, the trial steering committee, independent statistical center, sponsor functions, and sponsor management of CROs and third-parties involved in the trial
- Trial processes, such as randomization, maintenance of blinding, procedures for carrying out interim analyses, decision-making on adaptations, and firewalls
- Procedures for handling data, including data flow, data management, data storage, and data analysis reporting

Ball noted that the number of CDER BIMO inspections increased 17 percent in fiscal year (FY) 2009 to 788 inspections, after hovering between 647 and 690 inspections a year for the past five years. Ball said the number of CDER BIMO inspections will be about the same or increase slightly in FY 2010.

The majority of this fiscal year's inspections — about 450 — were clinical trial sites. About 100 were inspections of institutional review boards (IRBs), and another 80 were trial sponsors. "The number of sponsor inspections is increasing," Ball said. "Two-thirds are data validation inspection to compare what is submitted to what is at the trial sites."

She noted the number of warning letters sent to clinical investigators has increased significantly in the past few years from none in FY 2004 and 2005 to 18 in FY 2009. The number has risen from six in FY 2006 to 10 in FY 2007 and 12 in FY 2008.

Ball added that the Department of Health and Human Service's Office of Inspector General will soon release a report examining the challenges to FDA's responsibility to monitor and inspect foreign clinical trials.

Points To Consider When Responding to a Form FDA 483 or Warning Letter

Ball offered pointers in responding to FDA inspection reports and warning letters.

- If a citation is inaccurate, provide specific documentation to set the record straight.
- Accept responsibility, as appropriate.
- Indicate a clear understanding of the scope of the problem.
- If appropriate, conduct an internal audit of other studies to assess if similar problems occurred.
- If applicable, consider proposing both general and specific corrective action plans.
- Propose a general plan that addresses current and future studies.
- Consider whether standard operating procedures need to be developed or revised.
- Consider whether training is needed.
- Offer item-specific responses that contain strategies to correct specific problems, and make sure response tracks with individual items contained in the inspection report or warning letter.
- Consider including, if appropriate, a proposed timeline for corrections, including projected completion dates.
- Consider including, if appropriate, documents to demonstrate that adequate corrections have been made.
- Consider including, if appropriate, documentation of already completed corrective actions.

Other Recent GCP Developments in the Guide to Good Clinical Practice

IOM Recommends Complete Overhaul of NCI Trials Cooperative Group

Fewer Determination Letters Sent; Review, Consent Problems Persist

Group Works on Multi-Regional Research Ethics