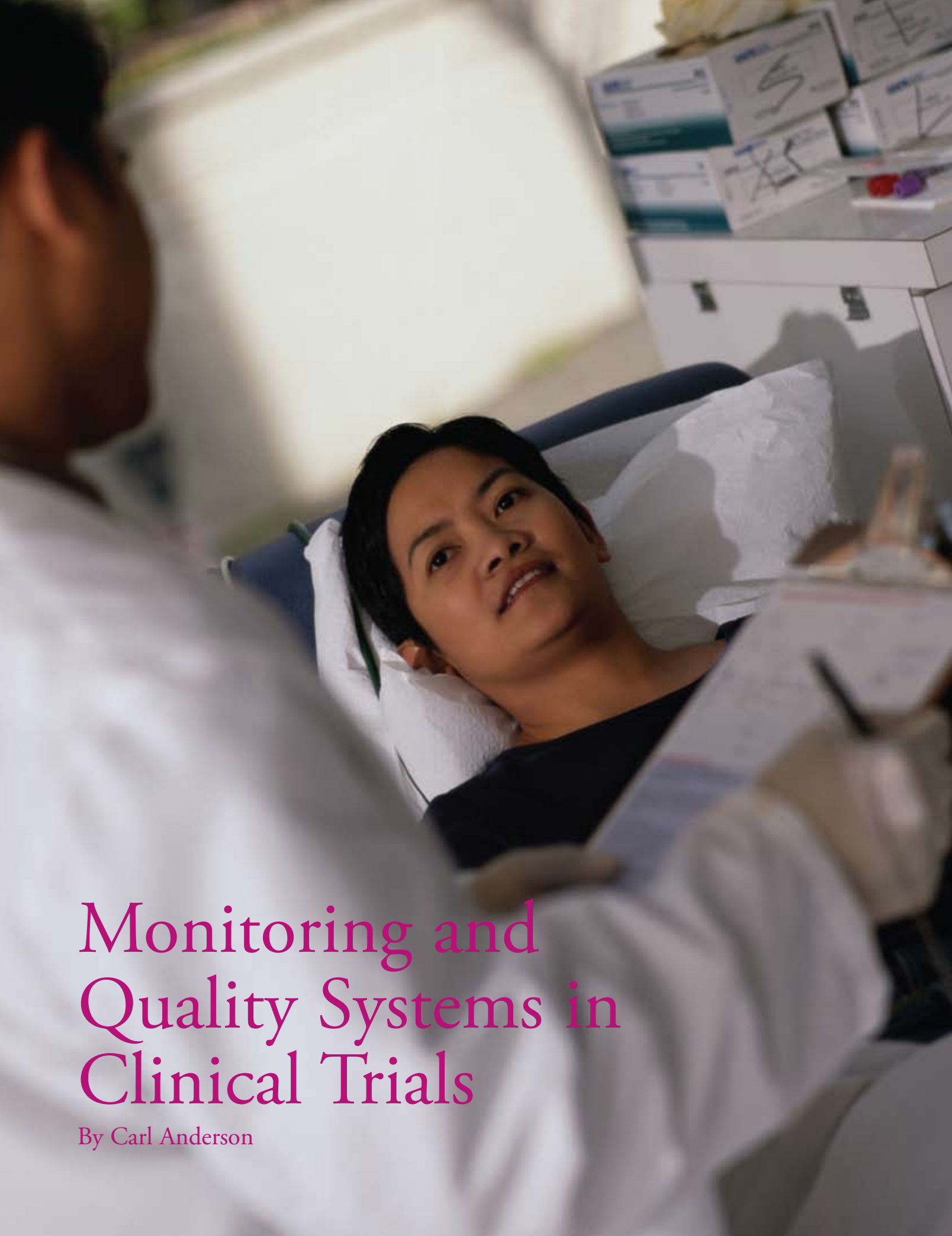

Monitoring and Quality Systems in Clinical Trials

By Carl Anderson

The enormous task of monitoring clinical trials is a primary regulatory responsibility and major expense for sponsors. This task is frequently contracted out to Contract Research Organizations (CROs), which remove it from the sponsor's direct control. Ultimately, however, the sponsor retains the regulatory responsibility. Recent FDA Warning Letters to clinical trial sponsors continue to cite "Failure to ensure proper monitoring of the investigation" among the top violations (**See Sidebar**). Unfortunately, the regulations are not specific regarding what sponsors should do to "monitor the progress of the investigation." The Investigational New Drug (IND) regulations do not require written procedures or a monitoring plan[1] (medical device regulations do[2]). This leaves sponsors with six key FDA guidance documents upon which to base their regulatory compliance plans.

FDA bioresearch monitoring managers have long emphasized the need for building quality systems into clinical trials.[4] Three principles are emphasized continuously:

- utilizing quality principals—developing an effective Quality Assurance Unit (QAU)
- using a risk-based approach—applying HACCP (hazard assessment critical control point) principles to clinical trials
- quality by design—building quality into the data lifecycle

One of the six guidances—the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *E6 Good Clinical Practice: Consolidated Guideline*[3]—is the primary guidance document on Good Clinical Practice (GCP) and outlines how to make Quality Control and Quality Assurance an integral part of an effective clinical trial.

An analysis of the six FDA guidance documents and 2007 Warning Letters to sponsors shows that developing effective quality systems is the best formula for GCP-compliant clinical trials.

FDA Guidance Documents on Monitoring Clinical Trials

Guidance for the Monitoring of Clinical Investigations[5] (1988) provides a concise description of the monitoring activities FDA expects from sponsors. It discusses development of a quality system including selecting monitors; establishing written monitoring procedures; conducting preinvestigation visits and interim visits; reviewing subject records; and completing written monitoring reports. It covers each stage of a clinical trial with the aim of building quality into the data lifecycle. The sections detailing selection of monitors and preinvestigation visits help sponsors develop a risk-based approach.

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees[6] (2006) defines these committees as "a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials." The document also defines other oversight groups including CROs that perform on-site monitoring and Institutional Review Boards (IRBs) that oversee the study. This guidance is useful in determining situations where a data monitoring committee should be used, which is certainly part of taking a risk-based approach.

Supervisory Responsibilities of Investigators[7] (May 2007) is still in the comment stage. For the first time, FDA outlines how a clinical investigator should supervise a study. This gives a sponsor concrete guidance on how much responsibility the investigator should delegate and what qualifications staff should possess. It also stresses the fact that activities not under the investigator's control, such as a central laboratory, remain the sponsor's responsibility. Again, understanding FDA's concerns at a clinical site and incorporating these concerns into monitoring activities represent a risk-based approach.

Computerized Systems Used in Clinical Investigations[8] (2007) was released after a lengthy review process that began in 2004. The document recommends listing each step in which a computerized system will be used in the protocol. It also recommends adopting Standard Operating Procedures (SOPs) to establish controls for computerized systems. Appendix A of the document is a list of recommended SOPs for computerized systems. This gives specific guidance on utilizing quality principles and building quality into the data lifecycle.

FDA and Clinical Quality Assurance

The next document is *E6 Good Clinical Practice: Consolidated Guideline* from ICH. This document unambiguously describes quality in the section on sponsor responsibilities (Section 5):

> "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 E6 document urges sponsors to build a quality system to ensure GCP-compliant research, recommending "quality control at each stage of data handling." In other words, quality is important throughout the data lifecycle. The most critical Quality Control activity is the clinical site monitoring visit. This guideline provides detailed recommendations for the monitor's activities. The recommendations emphasize the basics for successful monitoring, including:

- acting as the main line of communication between the sponsor and the investigator
- ensuring that the investigator and the investigator's staff are adequately informed about the trial
- verifying that the investigator has adequate qualifications and resources, including laboratories and equipment, to safely and properly conduct the trial
- verifying that the investigator is enrolling only eligible subjects
- verifying that source data/documents and other trial records are accurate, complete, up-to-date and maintained
- determining whether all adverse events (AEs) are appropriately reported
- communicating deviations and taking appropriate action designed to prevent a recurrence of those detected

In recent Warning Letters to clinical research sponsors, FDA cites at least one violation of these E6 monitoring recommendations. If repeated during a study, these violations illustrate a sponsor's failure to take the necessary steps to secure investigator compliance with the regulations. Both E6 and the IND regulations clearly state that the sponsor needs to terminate the investigator's participation in the clinical trial if compliance is not secured. After "Failure to ensure proper monitoring of the investigation," the next most common citation in recent FDA Warning Letters is "Failure to secure investigator compliance."

An FDA Warning Letter dated 5 March 2007, issued by the Center for Device and Radiological Health (CDRH),[9] states that a clinical investigator repeatedly failed to follow the investigational plan, including enrolling ineligible subjects and failing to perform protocol-required tests. However, the sponsor's work instructions to the investigator for monitoring did not address this continuing noncompliance. This sponsor was cited with both "Failure to ensure proper monitoring" and "Failure to secure investigator compliance."

Another FDA Warning Letter, dated 23 October 2007, issued by the Center for Drug Evaluation and Research (CDER),[10] determined that the CRO performing monitoring informed the sponsor of "significant problems" at a clinical site. The Warning Letter states that the sponsor did not investigate the problems. This sponsor also was cited with both "Failure to ensure proper monitoring" and "Failure to secure investigator compliance."

A third FDA Warning Letter, dated 26 April 2007, issued by the Center for Biologics Evaluation and Research (CBER),[11] found that the sponsor did not provide accurate information and cites an inadequate "Risk Evaluation" of clinical investigators and IRBs. E6 clearly states that the investigator and staff should be fully informed about the trial. Due to its potential to cause patient endangerment, the failure to inform researchers of essential information is taken very seriously by FDA.

CDRH is the center that historically has issued the most Warning Letters for sponsor responsibilities. In March 2007, the center issued three Warning Letters[12] to sponsors that cited them for "Failure to ensure proper monitoring." Two of these Warning Letters cited sponsors for not having monitoring procedures, a medical device regulatory requirement.

FDA Inspection Review

The sixth FDA guidance document is intended for FDA field investigators, not industry. FDA publishes a compliance program guidance manual for each type of inspection it conducts. For a sponsor, it is *CPGM 7348.810, Sponsors, Contract Research Organizations and Monitors.*[13] In Part III, "Inspectional," the agency details its instructions to the field investigator for selection of clinical investigators and monitoring procedures and activities. FDA field investigators perform these specific activities to ensure sponsors are in compliance with GCPs.

It is no accident that the document has many similarities to E6.

2007 Warning Letters

Following is a brief review of Warning Letters regarding clinical trials issued in 2007.

"Determine the sponsor's criteria for selecting clinical investigators."

The 23 October 2007 Warning Letter from CDER focused on a clinical investigator who had no prior clinical trial experience. A sponsor should monitor the rate of enrollment to ensure it reflects the intent of the protocol. The clinical investigator enrolled more than 400 subjects into the trial in three months. This should have been a red flag during management review of monitor reports and shows a lack of risk management.

"Review pre-trial and periodic site-visit reports." The 5 March 2007 Warning Letter from CDRH states that the monitoring reports "noted ongoing noncompliance with submission of CRFs (case report forms)" to the sponsor. E6 requires monitor reports to discuss deficiencies and what corrective actions are taken. Sponsors should have written Quality Control procedures for reviewing action items to determine whether there is systemic noncompliance. If there is noncompliance, there should be Quality Control procedures to raise the problem for management review and action if needed.

"Determine if the sponsor identified any clinical investigators who did not comply with FDA regulations. Did the sponsor secure prompt compliance? Obtain evidence of the prompt correction or termination by the sponsor."

This was cited in both the 5 March CDRH and 23 October CDER Warning Letters. Most monitors write letters to the clinical sites after visits. Such letters frequently list action items for the investigator to correct. However, the sponsor's responsibilities do not stop there; in fact, that is where they begin in securing investigator compliance. These letters frequently are not read by the clinical investigator. Clinical investigators, like most physicians, are busy professionals and often do not read routine correspondence. Letters are often filed by study coordinators without the investigator's review.

It may be necessary to involve senior managers or the medical director in direct discussions with the investigator. For serious investigator noncompliance, the regulations are clear. The sponsor should promptly secure compliance or discontinue shipments of the drug and end the investigator's participation in the trial. There are many factors to consider when taking such a step and senior management input is necessary. The sponsor needs clear procedures to ensure the appropriate managers are informed about serious noncompliance.

Finally, the CPGM requires review of the sponsor's Quality Assurance activities. Specifically, the field investigator is instructed to:

- determine whether the firm conducts QA inspections and audits
- determine how the QAU is organized and operates
- obtain a copy of any written procedures (SOPs and guidelines) for QA audits and QAU operation
- describe the separation of functions between the QAU and the monitoring of clinical trials

The 23 October Warning Letter from CDER references the sponsor's QA audits. However, the sponsor failed to take corrective action following the audits. Instead, the sponsor issued "memos to file," noting the deficiencies without correcting them.

FDA considers assessing a sponsor's Quality Assurance activities an essential component in any sponsor bioresearch monitoring inspection. There are no regulatory requirements for Quality Assurance in clinical trials, only the recommendations in E6. FDA specifically instructs field investigators *not* to request QA reports to encourage candid assessment of regulatory compliance and effective corrective action. The 23 October Warning Letter points out that a "memo to file" does not constitute corrective action.

FDA appreciates sponsors who have well-organized QA activities and a direct reporting line to senior management. The agency also encourages sponsors to seek independent assessments from outside specialists when there are ongoing violations of the regulations.

Conclusion

Each FDA Warning Letter documents a systemic

Searching FDA's Website for GCP Warning Letters

Reviewing Warning Letters provides a good sense of what the agency is finding in its GCP inspections. However, searching the FDA website can present a challenge. It has become more difficult because the site now displays only those Warning Letters issued during the past 12 months. Also, the three centers that conduct sponsor/monitor inspections do not coordinate the categorization of Warning Letters on the website. Knowing what to look for helps immensely in finding them. First, click on Warning Letters at the bottom of FDA's homepage (www.fda.gov), and then search Warning Letters by "Subject," listed alphabetically:

- *Bioresearch Monitoring Program/IRB*
  CDER Warning Letters to clinical investigators, IRBs and sponsors, and CBER Warning Letters to sponsors
- *Clinical Investigators*
  CDRH Warning Letters and some CDER Warning Letters
- *Institutional Review Board*
  CBER and CDRH Warning Letters
- *Investigational Device Exemption*
  CDRH Warning Letters to clinical investigators, IRBs and sponsors
- *New Drug Application*
  CDER Warning Letter citing sponsor for violations of 21 CFR 314, the NDA regulations. This Warning Letter, issued 18 January 2008, states that the inspection was conducted as part of the Bioresearch Monitoring Program and was signed by the Division Director of the Division of Scientific Investigations, which is responsible for GCP inspections.
- *Sponsor-Investigator*
  CDER Warning Letters
- *Sponsor Obligations*
  Archived CDRH and CBER Warning Letters not on the current webpage, i.e., more than 12 months ago

Each of these subjects would be used as a search term for archived Warning Letters more than one year old. Alternatively, for current Warning Letters, you can review all Warning Letters on all subjects issued in the past year by clicking on "…" at the far left of the Subject search screen.

CDRH Sponsor/Monitor Findings

In January 2008, the CDRH Division of Bioresearch Monitoring (BIMO) released its inspectional findings for Fiscal 2007. The top five deficiencies for sponsor/monitor inspections revealed a new entry, "Failure to submit progress reports." The top five deficiency categories were:

- Inadequate monitoring—39%
- Failure to submit progress reports—36%
- Failure to secure investigator compliance—27%
- Inadequate UADE analysis and reporting—27%
- Failure to inform investigators—21 %

BIMO also announced that the violation rate for sponsor/monitor inspections had shot up to 33% for the most serious inspection classification, Official Action Indicated (OAI), in Fiscal 2007, compared to 11% the previous year. CDRH conducted 40 sponsor/monitor inspections in Fiscal 2007.

breakdown in quality systems. In each case, one or more of the three key points—quality principles, a risk-based approach and quality by design—is shown to be lacking. In addition, the Warning Letter issued by CDER on 23 October 2007 involved deliberately fraudulent activity. That can be a worst-case scenario for sponsors. Intentional fraud is also one of the most difficult violations to uncover. That is why FDA managers stress the importance of building quality into a clinical trial system and not relying on inspecting quality after the fact.

Sponsors can safeguard their data by utilizing quality systems that emphasize the basics of Good Clinical Practice from the beginning. In the long run, frontloading quality is the key to ensuring data integrity and regulatory compliance.

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