Quality Assurance and Educational Standards for Clinical Trial Sites

Article two in this *Journal of Oncology Practice (JOP)* series, “Good Clinical Practice Research Guidelines Reviewed, Emphasis Given to Responsibilities of Investigators,” September 2008, described Good Clinical Practice (GCP) research guidelines, placing them into historical perspective, and discussed specific aspects of implementing the guidelines through the use of trained research professionals and well-written Standard Operating Procedures (SOPs). This series was inspired by publication of an American Society of Clinical Oncology (ASCO) statement in the May 20, 2008 issue of the *Journal of Clinical Oncology*, “American Society of Clinical Oncology Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites,” and described in the July 2008 issue of *JOP*. This third article discusses two of the exemplary attributes of clinical trial sites suggested in the ASCO statement—quality assurance and formal maintenance of high educational standards—and describes the contribution of these attributes to the optimum functioning of an effective clinical trial site.

Background on Quality Assurance and Education

As noted in the ASCO statement on minimum standards and exemplary attributes, implementation of internal quality assurance (QA) programs help ensure adherence to GCP guidelines and contribute to the ability of a clinical trial site to produce first-rate data. These programs should include conducting internal (self) audits, actively implementing and revising SOPs, recording protocol deviations, and initiating procedures to correct any shortcomings and prevent their recurrence. In addition to conducting routine self-audits, exemplary clinical trial sites should also submit to external audits to provide independent verification of the operations of their QA program. External audits can point out weaknesses in a QA program and provide suggestions for corrective action, which can improve the integrity of the trial site.

Implementation of an effective QA system relies on proper education of the entire trial site staff. ASCO recommends that all trial investigators in the United States be specialty board certified, and that international investigators obtain board certification when it is available. To fulfill GCP requirements, research support staff must have appropriate education and training for their particular roles in the trial process. GCP does not mandate certification of support staff (eg, clinical research associates [CRAs] and study coordinators), though providing evidence of the capabilities of these individuals to perform their job functions is desirable. Educational opportunities include training of personnel at the beginning of their employment to ensure they are familiar

with the operations, policies, and procedures of their particular research site. Continuing education is also important as policies change or deficiencies are discovered and need to be corrected. Many individuals involved in clinical trials, including investigators, may not have received formal training in GCP and other regulations required for clinical research, and the investigators are ultimately responsible for the conduct of their clinical trials. Certification and educational programs, including in classrooms and online, are available for research support staff (see box).

Best Practices for Quality Assurance Programs

“We have a robust auditing department as our QA function,” says Dee Anna Smith, CEO of Sarah Cannon Research Institute (SCRI), Nashville, Tennessee. SCRI enrolls approximately 3,500 patients per year on clinical trials, primarily in oncology. SCRI-affiliated physicians work within large oncology practices to put patients on clinical trials. SCRI provides quality oversight of the research program by setting guidelines and process and performing audits to verify compliance. “Training is a big component of QA,” Smith observes. “When you think about QA simplistically, you have SOPs and auditing, you are complying with the standards you set. Most people don’t do it. At the site level where most patients are entered on trial, there aren’t QA programs. Instead, the sites rely on pharmaceutical monitoring for compliance.” At Sarah Cannon, they have four individuals dedicated to Investigative Site compliance, and routine audits are utilized as training opportunities.

Smith sees QA as a constant fluid process that never ends. They are always looking for training gaps. When they audit, they are not necessarily looking for problems, but rather are looking at issues affecting the trial sites and how these present training opportunities. They classify the types of deficiencies detected by auditing of the research sites into three categories: procedural, significant, and critical. Procedural deficiencies are typically administrative-type errors and may include events such as documentation not being filed in the right place, which may reflect staff members not fully understanding the processes. With procedural deficiencies, these types of findings do not necessarily represent a departure from GCP and proper documentation practices. Significant deficiencies may represent a departure from GCP, but do not invalidate the data. An example of a significant finding may be a test being performed out of the protocol-required window, which needs to be reported as a protocol deviation. Procedural and significant deficiencies are findings in which the subjects’ rights, safety, and welfare have not been

compromised, and the data integrity has not been compromised. Critical deficiencies are the most severe, and occur when major departures from GCP and the protocol are discovered. These findings may have affected the subjects' rights, safety, and welfare, or their willingness to participate. In addition, data integrity may be affected. Clearly, prevention of any of these errors, particularly critical ones, is the aim of good QA procedures and training.

Marge Good, RN, BSN, MPH, OCN, is at the Wichita Community Clinical Oncology Program, a National Cancer Institute Community Clinical Oncology Program (CCOP) in Wichita, Kansas, which is a member of six cooperative groups. Good's practice is also looking at source documents and making sure patients who are enrolled meet eligibility criteria. Good says that one role of the nurse CRAs in her practice is to help investigators comply with the protocols; the physicians rely on them for this. In order to do this, the nurses need to understand staging and the importance of following the protocol-specified treatment regimen, among other things. This presents an educational opportunity to ensure the CRAs have the higher level of understanding and education to do their job. "More internal auditing will help us put our finger on the issues earlier," Good says, "so the staff doesn't leave because they are embarrassed and don't want anyone to know they didn't understand what they were supposed to be doing." Although the staff annual performance review includes a discussion of deficiencies, Good notes that they want to correct these problems early and to be more proactive in their auditing.

Standards for Continuing Education

Good says that much of the education at the Wichita Community Clinical Oncology Program is day to day, "New studies come along, and there are new ways to do things. Just by participating in studies, sites will understand new treatments better." They send their physicians and staff to research-based meetings to help keep them up to speed. "It's difficult to get the physicians to break away from their practices in the middle of the week because they have patients to see," she observes. "We try to get them to meetings to hear about the national perspective." There is also a push for more formal training, which, she says, takes a long time. They use a 10-module training program developed by the National Cancer Institute (NCI) and available to members of the clinical trial special interest group on the Oncology Nursing Society's Web site. The program covers what their nurses need to know about conducting clinical research, from the phases of trials to consent documents to accountability. Because some of the program is NCI-specific, the Wichita Community Clinical Oncology Program has used some of the material as templates to make their own research training manual. This fall they started formal training for their entire research staff that will include annual updates. All staff, including nurses, pharmacy, and other ancillary staff at the primary oncology practice they work with will be required to

Quality Assurance and Educational Resources

- National Cancer Institute: Standardized Case Report Form Work Group. https://cabig.nci.nih.gov/workspaces/CTMS/CTWG_Implementation/crf-standardization-sig

Society of Clinical Research Associates

- Certification and education for research staff: <http://socra.org/>

Association of Clinical Research Professionals

- Certification and education for research staff: <http://www.acrpn.net.org/>

Guidances for Institutional Review Boards, Investigators, and Sponsors

- Available at: www.fda.gov/oc/ohrt/irbs/default.htm

Oncology Nursing Society

- Available at: <http://clinicaltrial.vc.ons.org>

review and sign off on the training material. The Wichita Community Clinical Oncology Program has 13 sites across the state of Kansas, and there is one physician at each site one day a week, so they are always busy seeing patients. Good notes she is "at the top of the list" at monthly management meetings where she has the opportunity to interact with these physicians and introduce core pieces of the training program.

Smith noted that pharmaceutical companies continue to encourage continuing education efforts, and in a recent internal meeting, she says the team "talked a lot about principal investigator oversight and the influence of pharmaceutical companies. I have never felt those companies have had an undue influence." SCRI provides continuing education for research practices, and when they participate with sponsors, they may request that the pharmaceutical companies send medical science liaisons to the research sites to provide education about therapeutic agents. Much of the therapeutic area education for staff is delivered by SCRI physicians. Programs on-site can take the form of "lunch and learn" sessions, where the focus is on particular tumor types or disease processes and includes basic background information on common treatments and their historic context. These programs are for both physicians and research staff. The presenters use their own materials for these presentations. Sarah Cannon also has its own basic orientation program and may purchase other curriculum materials from outside sources.

Cost-Effective Implementation

As far as cost effectiveness goes, Smith says, "Online is the way to do it." At Sarah Cannon, educational programs are funded out of their operational costs. SCRI incorporates online Good Clinical Practice training modules, classroom training, standard operating procedure review, and job specific training. For GCP training, Smith says they "didn't want to reinvent the wheel," and turned to the University of Pennsylvania's training program. "We struggled to determine what is out there that represents best practices," she says. Webex-type online training programs as well as video conferencing and teleconferencing are used to provide investigator training and protocol-specific training. The advantage of a web-based program, Smith observes, is that participants can log in and follow the slide sets and ask questions in real time. Being able to access the slide deck ahead of time adds to the effectiveness of these programs.

The Quality Assurance department is currently implementing a Quality Management System (QMS). Document control, training requirements, and audit and result trending will be tracked and managed by the QMS. Using the QMS will assist in ensuring that required training is completed; audit results can be trended in real time, which will facilitate process improvements; and controlled documents can be housed, reviewed, and routed for approval electronically. The document and training systems will ease the burden of demonstrating compliance and can readily produce documentation to external auditors

Sarah Cannon has a full-time training and educational resource employee to facilitate adopting and using tools to improve job performance. This individual has prepared a

leadership reference manual that includes reading material, articles, and how-to and contact lists for new managers. Additionally, online modules, self study, and classroom training will be provided to emerging leaders as well as established leaders to assist in the development of and continuing education for SCRI management.

The NCI training manual that Good's group uses is free. However, one cost of training and compliance is the time commitment needed to do things properly. Good notes that regulatory compliance requires good processes and making sure that reporting and submissions are done in time so the site won't become noncompliant. "We are doing our patients a disservice by not submitting information in a timely manner." It also affects other patients across the country because of safety issues. Once the staff is educated on the importance of timely reporting, they see the need not to "get to it later." Good concludes it's an issue of time management and remembering why they are conducting clinical trials.

Upcoming Events

ASCO will hold conference calls in 2009 during which content providers to the series (including Marge Good and Dee Anna Smith) will discuss these topics in more detail and be available for questions. See ASCO's Web site at www.asco.org/researchresources for more information.

The next article in this series, to be published in the January 2009 issue of *JOP*, will cover survival tips for the audit process.

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