Good Clinical Practice Research Guidelines Reviewed, Emphasis Given to Responsibilities of Investigators: Second Article in a Series

The first article in this series[1] described the *American Society of Clinical Oncology (ASCO) Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites*. With this statement, ASCO recognizes compliance with Good Clinical Practice (GCP) guidelines as the minimum standard for conducting clinical research and identifies key characteristics of exemplary trial sites. This second article describes GCP guidelines and places them into historical perspective before specific aspects of implementing the guidelines—through the use of trained research professionals and well-written Standard Operating Procedures (SOPs)—are discussed.

GCP Background

Today's GCP guidelines are an international product of the World Medical Association's 1964 Helsinki Declaration, which specified the ethical responsibilities of researchers to trial participants; the US Food and Drug Administration's (FDA) codification of the Declaration's guidelines in 1978; and the 1995 International Conference on Harmonisation, which brought together regulatory agencies and industry associations from the United States, Europe, and Japan to agree on a unified international standard for conducting research, especially in trials evaluating new drugs.

The paramount importance of protecting participants in clinical research was recognized in the aftermath of World War II, and the first document to address the ethical conduct of biomedical research was the 1947 Nuremburg Code. The World Medical Association developed the Declaration of Helsinki using principles from the Nuremburg Code and the Declaration of Geneva, a statement on a physician's ethical duties, to define principles governing the ethics of medical research involving human trial participants. The principles of the Declaration of Helsinki are the foundation of the GCP guidelines. GCP is now considered the international ethical and quality "standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that involve participation of human subjects."

Together, these guidelines and international guidance define the network of interlocking obligations that trial sponsors and investigators use to safely and effectively design, conduct, and evaluate data from clinical trials.

Why GCP?

The goal of clinical research is to identify new standards of therapy in a well-defined, limited population to benefit the larger population. Ultimately, clinical trials are the only mechanism to prove that new therapies are safe and effective. Following GCP guidelines is a way to ensure that data generated by a clinical trial are accurate, verifiable, and reproducible, all of which are necessary to advance scientific knowledge.

Compliance with GCP also provides public assurance that the rights, safety, well-being, and confidentiality of trial participants are protected. Conducting research according the GCP guidelines is also the law. Ultimately, assuring the conduct of quality clinical trials is an obligation investigators have to participants that will ensure meaningful information for tomorrow's patients. (See box for specific FDA regulations.)

GCP in Cancer Clinical Trials

The National Cancer Institute of the United States funds the cancer Cooperative Group Program, which is a network of over 1,700 institutions and individuals conducting coordinated multicenter trials. The 12 cooperative groups are organized by specific cancer or treatment types and have expanded to include researchers in Europe, Canada, and South America. The pharmaceutical and biotechnology industry also oversee multicenter clinical trials conducted globally. One benefit of having clinical trials conducted across multiple sites is faster accrual of study participants, which can speed conduct of the trial and subsequent evaluation of data that may bring about the approval of improved treatments to the marketplace sooner than would a trial conducted in one place that did not support a large enough patient population to ensure adequate participation.

Because the cooperative groups and industry oversee trials conducted in many places at once, implementing GCP guidelines is one way of guaranteeing accurate data collection and consistent standards for conducting a trial spread wide geographically. The groups and industry use standard reporting, monitoring, and protocol development processes and build institutional review board (IRB) protections into each study protocol.

GCP Internationally

Because GCP is now an international standard, and because some larger trials are conducted not only in multiple centers but also in multiple countries, investigators' diligence in following GCP can mean the difference between a safely and effectively conducted trial and an improperly-designed, failed trial that takes time and resources but produces inaccurate data that cannot add to generalizable medical knowledge.

Researchers from multiple countries may be enrolling participants in a trial with a specific, defined protocol. The trial results can only be combined into a single analysis of the results if all the researchers at all the sites in each country are following the same guidelines. Researchers who want the opportunity to work on these large trials must show GCP compliance before they are invited to participate.

GCP in Practice

GCP guidelines may seem open to interpretation because they are declared, described, and codified in many different

places. For research staff, complying with GCP often means creating or adapting and adopting SOPs into every aspect of the site's research.

As an initial step, each investigator conducting biomedical research under a US Investigational New Drug Application is required to sign FDA form 1572 stating he or she will abide by GCP. This form should be signed only after an investigator fully understands the obligations of the position of principal investigator (PI). These obligations include total responsibility for local conduct of the trial, including all reporting requirements as defined by the FDA and the trial sponsor. Most PIs work with a team to conduct research, and the PI may delegate to team members, in writing, the authority to perform specific tasks. PIs cannot delegate the overall responsibility for the conduct of the trial.

Beginning clinical research does not have to be as daunting as it sounds. Even if not coordinated through a cooperative group, every trial has a sponsor, and the sponsor may have SOPs that guide the activities of local trial sites. Before a researcher begins a trial, she must have full, written IRB approval for the study protocol and, once the study begins, the ongoing and fully informed consent of every participant.

Every trial is monitored for compliance with GCP and study protocol. SOPs are the tools that evaluators (such as the FDA, the trial sponsor, or a cooperative group) use to determine whether a trial site is in compliance. "SOPs are critical. I can't emphasize that enough," states Robert Catalano, PharmD, who serves as Vice President of Regulatory Affairs for the Coalition of Cancer Cooperative Groups. PIs ensure compliance with trial monitoring by writing (or adopting) SOPs that describe every process that occurs within a trial, from enrolling participants eligible for the protocol to defining how and when laboratory tests be conducted. In some cases, SOPs are provided by the trial sponsor. In others, PIs may purchase commercially available SOP templates. The *American Society of Clinical Oncology Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites* was published with a sample list of SOP topics.

PIs may consider organizing their site's SOPs by functional area, staff requirements, or reporting requirements. Having a dedicated clinical research staff (or at least staff with dedicated hours) is crucial to following SOPs within a protocol. Putting thought into which person or position is best suited to implement each procedure can help to define processes. Future articles in this series will discuss the budgetary impact of matching staff to their most appropriate research activity, as well.

Often, a clinical trial site will be managed by a crucial member of the research team, the research coordinator. Certified by either the Society of Clinical Research Associates or the Association of Clinical Research Professionals, research coordinators know everything ongoing about a trial. They are not, however, responsible for the conduct of the trial. Sometimes a coordinator is so experienced at running a trial site that a new PI might not know all duties performed by that person. "It is imperative that the investigator is ultimately responsible," says Susan Devine, CCRP, of Toronto's Hospital for Sick Children. "If [investigators] don't know what a coordinator does, they should not be signing," (either the form 1572 in the U.S. or Health Canada's certification form) said Devine.

SOPs can also provide definition for how and when the PI and sponsor will regularly communicate with the trial's IRB. The PI is responsible for this regular communication, which is in place

Clinical Research Training Opportunities and Resources

FDA: http://www.fda.gov/oc/gcp/regulations.html

- FDA Guidances and Information Sheets for Investigators outline FDA's current thinking on specific research issues. Unless specific regulations are mentioned, these are only recommendations: http://www.fda.gov/oc/gcp/guidance.html
- Information about the way FDA makes and updates its rules: http://www.fda.gov/oc/gcp/preambles/default.htm
- Receive e-mail updates from FDA regarding changes in the law. Sign up at: http://www.fda.gov/oc/gcp/regulations.html

HHS/NIH/NCI Information sources:

- NCI Research Resources—a directory of research tools and services for cancer researchers: http://resresources.nci.nih.gov/categorydisplay.cfm?catid = 663
- NCI Cancer Trials Support Unit: http://www.ctsu.org/
- NIH Office of Human Subjects Research tutorials are available for research professionals: http://ohsr.od.nih.gov

Society of Clinical Research Associates–sponsored FDA Clinical Trial Requirements Regulations, Compliance, and GCP Conferences:

- Calendar at: http://www.socra.org
- SoCRA will soon be awarding CME credits for some of its trainings

SOP resources:

- Templates commercially available online, search clinical trial SOPs
- Norman Goldfarb's article comparing SOPs, available at http://firstclinical.com/journal/2005/0504_SOPReview.pdf

General resources:

From C-Change (Collaborating to Conquer Cancer) and the Coalition of Cancer Cooperative Groups:

- *The Elements of Success. Conducting Cancer Clinical Trials: A Guide.* http://www.c-changetogether.org/pubs/pubs/ClinicalTrialsSucess.pdf

GCP by US Law and International Adoption

Title 21 Code of Federal Regulations (CFR)

- Part 50 (requirements of informed consent) http://www.access.gpo/gov/nara/cfr/waisidx_01/21cfr50_01.html
- Part 54 (financial disclosure by clinical investigators) http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html
- Part 56 (responsibilities of an IRB-see article four of this series) http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html
- Part 312 (investigational new drug applications) http://www.access.gpo.gov/nara/cfr/waisidx_01/21/cfr312_01.html

Title 45 CFR

- Part 46 ("Common Rule" for protection of human research subjects) http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr.htm
- Helsinki Declaration: http://www.wma.net/e/policy/b3.htm
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines: http://www.ich.org
- E6(R1) Good Clinical Practice: http://www.ich.org/cache/compo/276-254-1.html
- E8 General Considerations for Clinical Trials (sponsor and investigator responsibilities): http://www.ich.org/cache/compo/276-254-1.html

to maintain the safety of trial participants. This is important because any PI is playing a dual role, both physician to his patient and primary investigator for a clinical trial. Being physician must come first; IRB involvement ensures this.

Obtaining informed consent from trial participants is an ongoing process throughout a trial—and not only in the case of new participants. During the conduct of the trials, the sponsor may require a change in protocol that requires newly informed consent statements for existing trial participants. Having SOPs that cover trial protocol and consent is a way to ensure that this process is followed correctly and consistently. This can be accomplished with thorough and ongoing training of site personnel. "Training site personnel in each protocol is one of the most important things to do" in clinical research, according to Dr Catalano. In her workplace, Susan Devine holds GCP/SOP trainings annually for all research staff. After a few years of training, she found that auditors monitoring the sites were much less likely to find discrepancies in complying with GCP guidelines.

Both Catalano and Devine emphasize the ongoing nature of training and GCP compliance within the structure of any trial. Because turnover in site personnel may occur during the course of a trial, having SOPs in place that describe procedures and requiring training of all personnel may be the only way to ensure that the trial is conducted consistently and accurately from beginning to end. Speaking of monitors' visits and the difficulties inherent in maintaining GCP, Devine adds that all of this information "is incorporated into GCP training." Catalano encourages researchers to adopt or adapt SOPs that describe "what they do" at the site rather than "what they would like to do." SOPs should be general enough so that they can be followed, but not so specific that using them becomes impossible. Devine uses a system of checklists in association with SOPs. These checklists help ensure that trial personnel are following GCP guidelines; if the checklist needs to be changed, that is a good indication that the SOP is not accurate as written and must be changed as well.

If you are considering entering clinical research, evaluate your site's ability to participate in clinical trials according to finances, size, personnel, and patient population. GCP guidelines do not change based on a trial site's size or resources. Each site must comply with the same standards. (See box for investigator resources and training opportunities.)

Complying With GCP Guidelines

Maintaining compliance with GCP guidelines requires constant diligence because of the dynamic atmosphere in which trials are conducted. Rather than considering this a burden, researchers and their teams can use compliance with GCP as a tool, a guide to the right thing to do. "There is no one way to comply with GCP," said Dr Catalano. He emphasized the importance of documenting each and every action within a trial, down to a daily diary of notes the PI would sign. "Documentation will allow a person (evaluator) to come in and independently follow the process of the trial, note any deviations from protocol and also the steps that the site took to remedy the situation." Besides meeting ASCO-affirmed minimum research standards, sites that make a goal of improving their research practices will find that GCP guidelines provide a solid foundation for attaining one (or more) of the defined exemplary attributes.

Preview of Upcoming Events

The next article in this series, to be published in the November 2008 issue of *JOP*, will cover quality assurance and continuing education as they relate to the smooth working of an effective, perhaps even exemplary, clinical trial site. See ASCO's Web site at www.asco.org/researchresources for more information.

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Reference

1. ASCO outlines minimum standards and exemplary attributes for research sites: Previews tools to be provided. J Oncol Pract 4: 185-187