Working With Your Institutional Review Board

This article is the seventh in a continuing series focusing on the exemplary attributes of successful research in clinical practice. In a statement published in *Journal of Clinical Oncology*, ASCO described a core group of standards and exemplary attributes for clinical trial sites.¹⁻³ The initial article of the series appeared in *Journal of Oncology Practice* in July 2008. This installment addresses how to work with institutional review boards (IRBs), covering the following elements of the ASCO statement: participation in the clinical trial development process and maintenance of high educational standards.

Background

As noted in the ASCO statement, “first and foremost, a quality clinical trial research site must protect the welfare and rights of all trial participants.”¹ A quality trial site must be compliant with the Good Clinical Practice Guidelines of the International Conference on Harmonisation,⁴ which are designed to protect participants in clinical trials. The ASCO statement also points out that “it is an essential responsibility of the principal investigator to interact with the IRB.” Successful interaction with IRBs is performed on the basis of an understanding of the responsibilities and procedures, including standard operating procedures, of both local and central IRBs.

ASCO Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

The ASCO statement addresses the minimum requirements for sites conducting quality clinical trials as well as attributes of exemplary sites. Both minimum requirements and exemplary attributes were determined on the basis of a review of the literature, current regulatory requirements, and consensus among community and academic clinical researchers. To conduct quality clinical research, sites should meet the minimum requirements. It should be noted, however, that the exemplary attributes are voluntary and suggested as goals, not requirements. Not all attributes will apply to all clinical trial sites, and many sites may be able to conduct high-quality clinical trials without accomplishing all attributes.

Working With Local IRBs

Helping local IRBs understand the many layers of scientific review conducted for trials funded by the National Cancer Institute (NCI) provides investigators with an important opportunity. Scientific, safety, and risk-versus-benefit issues involving the study population as a whole have been carefully

considered by cooperative groups, the NCI, and the US Food and Drug Administration (FDA). Local IRBs may have more uncertainty about earlier phase trials. By their nature, these trials have more limited data on efficacy and pose greater risk to participants. As Peter Paul Yu, MD, Palo Alto Medical Foundation (Mountain View, CA), observes, “Presenting phase II trials to the IRB is more challenging if there is a data void.” Because they are usually conducted on the basis of preclinical rather than clinical data, phase I trials may present even greater challenges; it may be impossible for some investigators to initiate such trials locally if they seem too dangerous to patients in the view of the local IRBs. Although phase I studies were often seen as toxicity-defining trials in the past, with today’s targeted therapies and biomarker identification, they need not be considered synonymous with toxicity. James Atkins, MD, Southeastern Medical Oncology Center (Goldsboro, NC), says that although local IRBs should consider local issues, “my belief is that most people are similar in nature, so there will not be many differences between geographic areas.”

One important role of local IRBs is to review adverse events (AEs). In federally sponsored research, guidance from the Office for Human Research Protections (OHRP) clarifies that investigators are required to report AEs that are unanticipated problems, defined as meeting all of the following criteria: unexpected (in terms of nature, severity, or frequency) given the research and study population, related or possibly related to participation in the research, and suggestive that the research places participants or others at a greater risk of harm than was previously known or recognized.⁵ The OHRP states that a “vast majority of adverse events occurring in human subjects are not unanticipated problems” and therefore do not need to be reported. However, all unanticipated problems—regardless of whether they are AEs—must be reported.

The FDA has also issued guidance on distinguishing those AEs that are unanticipated problems and must be reported.⁶ AEs are only unanticipated problems if they are “unexpected, serious, and would have implications for the conduct of the study.” The FDA goes on to state that “an individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. . . . The major exceptions to the general rule that an isolated event is not informative are serious AEs that are uncommon and strongly associated with drug exposure.”

Both investigators and IRBs need to understand that AEs at their sites must be reviewed and reported in a timely fashion. In the case of a multi-institutional trial, there may be large numbers of AEs reported worldwide, and local IRBs may be flooded with reports from all studies using the investigational

drug. Particularly with already approved agents, AEs might be associated with use in settings other than oncology. These events might be less clinically relevant to the oncology studies being conducted locally. The FDA and OHRP guidance recognizes that investigators and IRBs at individual sites have difficulty assessing the significance of AEs occurring across the entire trial. Both agencies acknowledge that sponsors are in the best position to review the significance of AEs. The FDA requires sponsors to submit reports and analyses to investigators and the administration and permits sponsors reporting directly to IRBs to fulfill investigators' requirement to report to the IRBs.

As Marge Good, RN, MPH, Wichita Community Clinical Oncology Program (Wichita, KS), points out, local IRBs may meet infrequently, and if they do not have a quorum, they may have to postpone a meeting. They also have deadlines for submission of protocols to discuss, so investigators need to anticipate these issues, which have the potential to delay access to studies. Local IRBs will want to see protocols and consent forms, including those with language that is community specific. IRBs may have limited budgets, so investigators should be prepared to provide multiple copies of all review materials for the boards.

Good also emphasizes keeping open the lines of communication between investigators and local IRBs. One aspect of this involves reviewing protocols and consent forms with an eye toward local issues and fixing any problems preemptively. Investigators should make sure they have educated themselves on OHRP and FDA guidelines and submit all required documentation. Good recommends keeping in mind that IRBs exist to protect patient safety. "With our own IRB, things are never perfect. Someone is always suggesting rewording so patients can understand things better," she says. The IRB also examines economic costs to participants that may be associated with clinical trials, particularly related to insurance coverage or lack thereof. Good suggests, "The biggest help in maintaining communication is to keep it as positive as possible. If the IRB has no suggestions for change, they are probably not doing their job." Some IRB offices are making staff available for consultation with investigators to facilitate early and informal communication while IRB materials are being developed. Taking advantage of this open-door policy may help investigators ensure complete submissions and avoid problems with issues to which IRB members pay particular attention.

Challenges Involved With Review of Oncology Trials

Local IRB members include health care professionals (eg, physicians, nurses, and pharmacists) and may include community representatives, patient advocates, attorneys, ethicists, and representatives of religious organizations or others with spiritual backgrounds. It may be a challenge,

however, for IRBs to assemble members with expertise in clinical trials in oncology. "My observation is that local IRB members are placed in a difficult situation," says Yu. "They are charged with evaluating complex scientific studies to weigh the potential risks and benefits for participants, including potential societal gain." Because local IRBs include members who may not have the ability to judge potential scientific benefits of a study, the focus is often on potential harm to patients. "For oncology patients," Yu explains, "there is a lot of harm that oncology drugs can do, which puts the local IRB in a difficult position, compounded by the difficulty [in] distinguishing drug toxicities from the effects of the cancer itself." Many local IRBs may be more familiar with studies outside of oncology, the risks of which are not as significant as those posed to participants in oncology trials. Lay members of local IRBs may not understand oncology trials from the point of view of patients with cancer, who may have few other options. The patient advocacy community has been a strong supporter of cancer clinical trials and views access to investigational treatments as a critical part of patients' care plans. It is important for IRBs, Yu says, to understand the unique perspective of patients with cancer.

The NCI Central IRB Initiative

The NCI initiative regarding central IRBs (CIRBs) was established in response to the heavy administrative burden in the cancer clinical trial system resulting from the need for IRB review at every site of multisite trials, which often involve hundreds of sites.⁷ Under the CIRB model, the CIRB conducts the full-board review of a protocol. The protocol, the CIRB-approved consent form, minutes of meetings, and any other relevant review documents are posted on the private side of the CIRB Web site. Local IRBs access these documents, and local IRB chairs and/or subcommittees review them for any local context issues. This local review process, known as facilitated review, does not require the full board to meet and can occur within days of the investigators' request for review. If there are no local concerns, local IRBs notify the CIRB, which becomes the IRB of record for the study, reviewing amendments, conducting continuing review, and reviewing serious AEs. Local IRBs no longer need to conduct these reviews (except for when serious AEs occur at their sites). This initiative involves two CIRBs: the adult board, which reviews all phase III adult cooperative group trials, and the pediatric board, which reviews children's oncology group phase II, phase III, and pilot studies. The NCI CIRB Initiative resource box in this article lists links to the public side of the CIRB Web site, including contact and enrollment information.

Good sits on the adult CIRB as a member. Some local IRBs meet infrequently, so facilitated reviews that do not require participation of the full local IRBs mean faster trial initiation for local investigators. The CIRBs are able to assemble national experts with oncology expertise, including not only oncologists, radiation therapists, oncology nurses, and

pharmacists but also consumer (patient) advocates, ethicists, and statisticians. Yu points out that his local IRBs take “great comfort” in knowing a protocol has been reviewed by the CIRB. They can read the minutes and how the review took place, the questions that were raised, and the answers. They can also gain reassurance that the study has value and that toxicity and other concerns can be handled appropriately. In addition to this benefit, Good also notes, “Oncology experts in our community would not be able to participate in our local IRB review of oncology trials because they would also be accruing to the trials, which is viewed as a conflict. Having the outside expertise of the CIRB removes this problem for our local IRB.”

Regional and Commercial IRBs

Institutions, practices, and industry sponsors may use regional or commercial IRBs to review multisite trials. For example, some institutions are forming research consortia to either create a multi-institutional IRB or rely on one another's IRBs to review protocols opened at all the institutions. Some investigators may make use of commercial IRBs, but there may be local or institutional regulations prohibiting investigators from using them. Atkins notes that commercial IRBs charge for their services, but the pharmaceutical companies sponsoring trials should cover this expense, and they are likely to select commercial IRBs with good track records and reputations.

Looking Ahead

ASCO's Exemplary Attributes Subcommittee is discussing development of resources to assist researchers in working with their IRBs. This may be accomplished in conjunction with other organizations or with federal government input. Yu points out that although there is a need to conduct outreach to IRBs, this must be accomplished outside of the evaluation of a specific clinical trial and will require extra effort as well as receptive IRBs. Yu envisions that resources for this effort might include a Web site with Webinars or documents that local IRBs and investigators could use for training and reference, possibly with examples of trials and case studies to illustrate the issues unique to cancer trials.

Upcoming Events

ASCO will hold conference calls in the fall of 2009, during which content providers to this series will discuss these topics

References

1. Zon R, Meropol NJ, Catalano RB, et al: American Society of Clinical Oncology statement on minimum standards and exemplary attributes of clinical trial sites. *J Clin Oncol* 26:2562-2567, 2008
2. ASCO outlines minimum standards and exemplary attributes for research sites: Previews tools to be provided. *J Oncol Pract* 4:185-186, 2008
3. Zon R: Guidance for quality research. *J Oncol Pract* 4:186-187, 2008
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH guidelines. <http://www.ich.org/cache/compo/276-254-1.html>

Resource: The National Cancer Institute Central Institutional Review Board Initiative (www.ncicirb.org)

The central institutional review board (CIRB) initiative is sponsored by the National Cancer Institute in consultation with the Office for Human Research Protections of the Department of Health and Human Services. The initiative provides IRB review for all phase III adult cooperative group trials as well as phase II, phase III, and pilot cooperative oncology group pediatric trials. It is designed to reduce the administrative burden on local investigators while maintaining high standards of protection for clinical trial participants. By using the review process facilitated by CIRBs, local IRBs and investigators can enroll participants onto cooperative group clinical trials much faster.

To learn how the CIRB process works, including links to local responsibilities and requirements, visit www.ncicirb.org/CIRB_HowWorks.asp.

To explore joining the CIRB initiative, including 30-day Web site access for your local IRB as well as a comprehensive enrollment packet, visit www.ncicirb.org/CIRB_join.asp.

To have your questions answered within 24 hours, call the help desk toll free at 1-888-657-3711 or e-mail ncicirbcontact@emmes.com.

To view the searchable database of CIRB-approved studies, visit www.ncicirb.org/CIRB_Protocols.asp.

in more detail and be available for discussion. Visit ASCO's Web site at www.asco.org/ClinicalTrialResources for more information. The next article in this series, to be published in the November 2009 issue of *JOP*, will discuss enhancing participation in the research process.

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5. Department of Health and Human Services: Office for Human Research Protections: Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.pdf>
6. US Food and Drug Administration: Guidance for clinical investigators, sponsors, and IRBs: Adverse event reporting to IRBs—Improving human subject protection. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127346.pdf>
7. National Cancer Institute: Central review board initiative. <http://www.ncicirb.org/>