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What's New in GCP?
FDA Hears Recommendations on Updating Trial Regs

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When the FDA asked the public for recommendations in modernizing its regulation of clinical trials in a public hearing April 23, several long-standing concerns — adverse event reporting, harmonization, the use of central institutional review boards, informed consent — were presented, but a couple of new issues also surfaced.

"The agency is interested in feedback on specific good clinical practice regulations, policies and practices that may need clarification or revision to facilitate advances in the ways that clinical trials are conducted, removing impediments to the use of innovative approaches, and otherwise improving the conduct of clinical trials," Kathleen Uhl, the medical director for the Center for Drug Evaluation and Research's (CDER's) Office of Medical Policy, said in opening the meeting.

One of the new topics presented was clinical trial audits. Matthew Weinberg, CEO of the Weinberg Group, which is the leading independent auditor of clinical trials, said that the FDA should mandate "systematic audits of all clinical trials" and that the auditors "should be independent from the [contract research organizations (CROs)] that conduct those trials."

He noted that "none of us, I suspect, would buy a stock from a company that we thought didn't have audited financials, and yet, we buy healthcare products in which the data that was presented is not audited by regulation. We hope the companies are doing it."

Weinberg said that "it is not a question about whether or not we constantly find fraud; it is a question about whether or not we can rely upon the data we get because it has been audited and produced in an acceptable manner."

He said auditors should be chosen by the sponsor and not the CRO and that CROs "should be prohibited from auditing data derived from trials that they conduct. They could audit each other, but they shouldn't necessarily audit themselves."

Weinberg asked the FDA to issue regulations requiring trial auditing on a regular basis by "auditors who have the same level of independence that we expect from our stocks, and therefore we would have conflict-free, trusted data."

Weinberg was asked whether the audit results would be available to regulatory authorities. He said it should be handled the same way as the results of manufacturing audits. "The inspectors have the right to look at that data and see what has been found. The same logic would transfer to this. If you are going to have GCPs, then you ought to apply the same standards that you do to everything else."

In another presentation, Andreas Koester, head of clinical trial innovation at Janssen Pharmaceutical, noted the agency has pointed out that sponsors and CROs are "reluctant to change the processes related to clinical trial oversight and management because of uncertainty about whether new processes would be in compliance with applicable regulations." Koester proposed sponsors submit an integrated end-of-Phase 2 quality management plan to the FDA that would describe all sponsor oversight activities for the agency's review and comment. "This integrated quality management plan, specific for the

study and the compound under investigation, should then serve as the basis for FDA inspection," he said.

Koester added that the quality management plan should be voluntary and include a description of central oversight of the trial, the monitoring plan, the auditing plan, and the overall quality plan.

Reducing Adverse Event Reporting

Marta Fields, director of compliance and quality systems with Seattle Genetics, said that the FDA guidance regarding adverse event reporting to institutional review boards should be applied in sponsor reports to investigators.

The change, she said, "will ensure that the important safety information that is really necessary is promptly communicated to participating investigators, while ensuring that it doesn't get lost in the volume of information that the investigator must review." In addition, "this approach will ensure timely and consistent reporting to the IRBs, since they will be receiving the same information that is provided to the investigator."

She noted that the requirement to provide individual case reports to the FDA would remain unchanged. The information in the individual safety reports would still be provided to investigators but in aggregate form when the Investigator's Brochure is revised, which is at least annually and more frequently when important safety information is found.

Robert Temple, CDER deputy director for clinical science, noted the revision of safety reporting rules "requires rapid reporting only of serious, unexpected adverse reactions... Doesn't that go some distance toward doing what you are hoping to accomplish?"

"I would like to say that it does, but it really doesn't," Fields responded, noting sponsors "take a very conservative approach to this [and] would rather over-report than under-report... I think it needs to be more explicit."

Cami Gearhart, chair of the Consortium of Independent Review Boards, noted the FDA's revision of 21 C.F.R. Parts 312 and 320 "has improved the nature of information that IRBs are receiving" but that those regulations affect only a small part of "the giant engine that generates IND safety letters across the clinical trial community."

"We are still receiving thousands of IND safety letters a month," Gearhart said. Sponsors and investigators interpret 21 C.F.R. Part 56 "to require every investigator on multisite studies to send every IND safety letter to the IRB... As long as Part 56 requires every investigator to send in unanticipated problems, which are often interpreted to include every IND safety letter, we are going to struggle with stemming the flow from sites."

She noted the Consortium is working with sponsors and sites to streamline the reporting process. "There are a number of mechanisms that we can use to designate one site or even the sponsor to send the IND safety letters" to the IRB.

Gearhart recommended FDA consider revising 21 C.F.R. Part 56 "to clarify and establish the sponsor's obligations in communicating with the IRB." She noted that, under 21 C.F.R. Part 812, medical device sponsors are required to report to the IRB, "but there are no similar obligations under Parts 312 and 320 for pharmaceutical manufacturers."

In addition to clarifying the role of sponsors, especially in multisite trials, Gearhart said FDA should "indicate that individual investigators are relieved from the burden of just passing on safety letters."

"It would be nice to have some uniformity between the definitions in Parts 312 and 56," Gearhart added. "It would be nice to have explicit clarification."

"So unanticipated problems could be designated as not including safety reports that have already been sent to the IRB," Temple noted.

Harmonization Needed

Christine Chung, a member of the American Society of Clinical Oncology's (ASCO's) cancer research committee, said the group wants FDA and other federal agencies that oversee clinical research to "develop uniform policies across all types of research." Specific areas ripe for harmonization, Chung said, are conflict of interest disclosure, adverse event reporting, privacy requirements and standards, and uniform terminology for central IRBs.

Chung noted that, in ASCO's response to the Department of Health and Human Services' Advanced Notice of Proposed Rulemaking to revise the Common Rule, the group called for all Common Rule agencies to issue a single set of guidances. "ASCO believes that the proposal has a significant potential to improve the process of conducting research that is subject to the oversight of multiple federal agencies," she said. "Greater consistency in regulations, guidance and interpretation would be beneficial for researchers who want to follow the rules but may be confused by the process."

Gearhart also called for harmonization of federal financial conflict-of-interest reporting thresholds, noting that the FDA level is $25,000, the HHS threshold is $10,000, and the new NIH guidelines are $5,000. "It is confusing for investigators to keep track of what they are supposed to be reporting, and it risks confusion for IRB staff to keep track of the sponsoring organization and at what level we are assessing their conflict of interest. It would be welcome to have some uniform requirement."

Jennifer Holcomb, vice chair of the Association of Clinical Research Professionals (ACRP), said "harmonizing various inconsistencies in documentation of informed consent between FDA and [International Conference on Harmonisation (ICH)] would be most welcome... ICH guidelines and FDA regulations are not as consistent as we'd like them to be. There is a little bit more specificity defining data, data storage, data use, and conduct rules in studies under ICH guidelines."

Informed Consent Reform Needed

Holcomb added that "ACRP has come to believe that what is truly needed is reform of the informed consent process. ACRP believes the informed consent process should be addressed in its entirety; not just the form itself... To maximize the efficiency of a robust informed consent process, ACRP believes that it is essential to ensure those who are conducting informed consent, regardless of their role, have demonstrated appropriate competencies."

ACRP recommended minimizing and streamlining the informed consent form "to simply document that the process has occurred and really invest the time and effort at credentialing and ensuring that we have qualified professionals with appropriate training carrying out the process."

Rene Cabral-Daniels, representing the National Patient Advocate Foundation and Regulatory Education and Action for Patients, said "the informed consent process should be simplified for subjects participating in clinical trials. It may be possible to achieve this goal by having a template that would harmonize the process across domestic and international study sites. Using a single informed consent process for all subjects in a multicenter study would ensure that they all receive the same information and have access to the same educational resources. Informed consent also should be made more efficient and patient friendly to ensure the proper education of subjects in such trials, using different types of tools to give patients information via different media. These tools could include a study subject bill of

rights, a clear list of subject responsibilities, and informed consent videos that clearly explain the process and terminology."

Cabral-Daniels added "the best interest of the patient should guide future deliberations by serving as the keystone upon which decisions will be made." However, "the best interest of the patient is not limited to safety concerns. While patient safety concerns are important, the best interest of the patient might include allowing the patient to assume an appreciable risk if he or she is confident that such risk assumption is worthy of the potential it generates, no matter how spurious that hope may be in clinical terms."

She recommended the FDA require that study results be communicated to trial subjects "in an accessible way. Human subjects should not be treated as just another piece of study 'materials,'" Cabral-Daniels said. "Simply referring participants to the raw data results posted on ClinicalTrials.gov is not adequate, as the majority of patients would not be able to digest those results and data. Sponsors should be required to send an explanatory letter to the subjects who participated in the trial after the trial is completed. The letters should let those subjects know — in accessible and plain language — the outcomes and the long-term impact of the study."

Koester suggested adding the number of subjects enrolled, the dropout rate, and the amount of missing data to the result records in ClinicalTrials.gov to increase clinical research transparency.

A representative of the American Association for the Advancement of Science said more attention should be paid to patient-generated health registries. "Some of these registries have as their main purpose the recruitment of patients for clinical trials," she said. "Other registries are for people who have a disease or a family member with a particular disease."

The AAAS representative noted that registries as recruitment tools "are going to create some real challenges" for the FDA "because of biases that might be inherent in them."

FDA Needs To Push Central IRBs

Jennifer Kerr, vice president, clinical research for Cook Medical, recommended that the "FDA require institutions to accept an approval by a central or national IRB when a sponsor has chosen to use this approach. We would also encourage the FDA and HHS to review the regulations governing the IRBs to ensure that they allow for institutions to accept national IRB determinations.

"Our hope is that a central IRB determination could be issued to a local IRB and, at that particular point, it would be more administrative" in supervising the study at that institution, which is "what we experience outside of the United States."

She also recommended that the FDA develop guidance on the content of subject recruitment materials. "Because this material must be approved by each IRB, often there are varying expectations. Guidance would provide sponsors and IRBs with a framework to develop and approve acceptable materials in a more timely manner," Kerr said.

Gearhart noted that subject safety can be "much more effectively protected...when one IRB has jurisdiction over all of the sites" in a multisite clinical trial. "For example, at continuing review, we generally ask sponsors for aggregated data regarding the safety profile of the study. At a multisite study level, we have no problem receiving this information because, of course, we have the authority to shut down the whole study. But when we are working with a single site, we can ask for the same information, from the same sponsor and have trouble getting it. We just don't have the leverage."

She noted that an IRB "with oversight of multiple sites has more authority and leverage to effect meaningful amendments to a study or to collect meaningful information, or to ensure that the consent form is comprehensive, thorough and consistent among sites."

Koester noted that "multiple IRB reviews mean duplication of effort, increased expense, and...a dilution of responsibility, as no single IRB feels empowered to make protocol changes." He said FDA guidance "is needed to clearly delineate the role of local versus central IRBs, ideally on a level that allows for global harmonization."

Gearhart added that "it is very unclear the extent to which Part 11 applies to IRBs." She noted that an IRB had received a 483 for non-compliance with electronic signature requirements. "Just the indication, the suggestion, the possibility that Part 11 could apply to us, leads our customers — the pharmaceutical companies and CROs — to expect us to comply with Part 11," she said. "So long as this lack of clarity exists, we feel that we are compelled to comply."

FDA Needs To Encourage Electronic Systems

Noting that medical product companies have a "terrible fear of change and what the regulators will do," Joles Mitchel, president of Target Health Inc., said that, in the use electronic records in clinical trials, the "FDA is not a barrier. In fact, in many areas, the FDA is actually ahead of the game."

"With the advent of [electronic data capture (EDC)] and other electronic tools, including electronic trial master files, and the ability to enter clinical trial data directly into EDC and [electronic health record] systems, it seems silly for our industry to spend a lot of money and time to monitor paper records transferred electronically, rather than using electronic records as original data," Mitchel said.

However, "FDA inspectors need to be retrained, and that is something that FDA is doing. They have to accept what is acceptable and risk allowing errors of omission and commission. There are going to be errors. There have to be errors. In fact, if there aren't any errors, you'd better worry."

Mitchel said FDA inspectors should have criteria for determining acceptable and reasonable errors of omission and commission that do not affect patient safety or data quality and "focus more on assurance of compliance," such as whether the researchers were trained properly, the drug and device supplies are accounted for, and potential conflicts of interest. "It is not so much 'did I fill out the financial disclosure form properly' but 'is there any problem with conflict of interest and possible fraud,'" he said.

Royce Heslip, the CEO of Aptia Systems, Inc., noted his company interviewed 40 research coordinators and found that keeping track of the paperwork "was probably the biggest complaint and frustration. So often they would find the [informed consent] forms were incomplete — boxes weren't checked or signatures might be missing. And, of course, forms get lost."

The second most common complaint was that "the paperwork just really gets out of hand. Just carrying around stacks of paper with the risk of unauthorized people looking at it was something that concerned them. Just trying to keep track and organizing all that paperwork was quite a chore and something that they could quickly get behind on."

Another concern was regulatory compliance. "With so many rules out there, the coordinators are just thinking between the state and federal rules — whether they are getting it right," Heslip said.

He said electronic systems could help, and suggested "a handheld device to document informed consent, comply with federal regulations, minimize risks, reduce paperwork, and better inform research subjects."

He said a tablet could include a video presentation of the information needed to be conveyed in the informed consent process, followed by questions "to make sure the subject really did comprehend what was being discussed." The video and questions also could be available in numerous languages.

As for privacy and security concerns, "tablets have passwords and other ways to control [access], and even if it is lost or stolen, there are ways to remotely wipe the data and that is far better than a clipboard or paper files."

The form itself could be signed with an electronic signature and, by using a portable printer, a copy could be given to the consented subject.

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