Report on RESEARCH COMPLIANCE

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In Busy Meeting, SACHRP Adopts FAQs, Discusses Sharing Results

A subcommittee of the Secretary's Advisory Committee on Human Research Protections will take a closer look at the related topics of sharing with study participants findings about their health uncovered during a trial and providing them the outcomes of research trials.

SACHRP assigned its Subpart A Subcommittee the task of developing recommendations on returning individual and aggregate research results to participants after hearing from a panel of speakers at its March 8–9 meeting in Washington, D.C.

Gathered for the first of its three yearly meetings, SACHRP advises the Office for Human Research Protections by making recommendations to the Department of Health and Human Services, of which OHRP is part. Typically, its recommendations are sent to HHS, and, if adopted by HHS, are then forwarded to OHRP for action.

The committee also approved two sets of frequently asked questions, developed by its Subpart A Subcommittee, focusing on documentation of informed consent and "parental permission and assent of children." These were developed by the same subcommittee that got the new assignment.

The new FAQs address areas that have been the source of administrative struggles for institutional review boards, which may have led to inconsistent decisions and caused over-regulation that "went beyond the requirements," SACHRP Chair Barbara Bierer told *RRC*.

"This was very much an attempt to make sure that people understood the flexibility of the regulations," said Bierer, professor of medicine at Harvard Medical School and senior vice president for research at Brigham and Women's Hospital.

'Incidental' Findings May Be Important

Much of the meeting was devoted to the issue of returning findings from a research study to participants. The discussion was divided into two parts, and SACHRP heard speakers who addressed sharing information discovered about an individual that is unrelated to the purpose of the study and sharing aggregate results, endpoints, conclusions or outcomes of the study with subjects.

"Distilling the conversation, we decided this was really a time for further discussion. We are going to refer the practical issues to the Subpart A Subcommittee to come up with recommendations on guidelines on sharing of research results that are the topic [of the research] and those findings that are incidental to the research," Bierer said.

For example, if a subject is discovered, through a screening process that is done before any intervention involved in the study, to have high blood pressure, for example, or a chest X-ray detects an abnormality, or a gene such as BRAC1 that is linked to cancer is revealed, should the subject be told? These were the kinds of questions that were discussed, Bierer said.

Also discussed were how such information would be communicated, whether it should go to the individual or a caregiver, would permission from the subject be required before such information is shared, and whether there is a duty or obligation to return such information.

"We didn't come up with recommendations," Bierer said. "But all of us felt strongly that if something is clinically significant…actionable, then one can think…we do have a duty to inform."

"It was a very interesting and prolonged discussion," she added, "because it is very hard to come up with a set of rules that works for every situation and is not dependent on facts. And something that might be relevant in 2011 might be considered very differently five years from now, or five years ago."

Source of Result May Be an Issue

This brings up a related issue —"How long do you maintain the data?" Bierer said.

Bierer also noted there is a concern about the validity and reliability of these ancillary findings that can come up in trials if a lab may have been used that is not compliant with the Clinical Laboratory Improvement Amendments law. Bierer said she personally is concerned about whether the possible return of incidental findings means that each test must be read by a "professional," such as whether a radiologist must be the

one reading images, which could add great expense to trials.

Findings from non-CLIA-compliant labs may be shared with investigators "in a research setting, but you are not supposed to tell a patient" the results, Bierer said.

The other part of the discussion concerned "how you share the knowledge from the research itself," Bierer said, including whether there is a benefit to sharing results, whether patients want to know and how the results would be communicated. Other factors that come into play are when the participant is intellectually impaired and whether relatives of individuals should be told as well.

One of the presenters was Deborah Zarin, M.D., director of ClinicalTrials.gov, who Bierer described as "very thoughtful about the benefits and the challenges" of describing research results in a useful, and accurate, way for the benefit of individuals.

As of the end of February, some 130,000 trials were registered, but only 3,000 have results posted with them. Zarin told SACHRP that 350 new trials are registered every week, but "most of them are not the kind we're thinking of," Bierer said. "Very few are transformative trials."

FDP Reps Describe 'Wonderful' Projects

SACHRP also heard presentations from members of the Federal Demonstration Partnership, a collaboration among approximately 120 research universities and 10 federal agencies (*RRC* 3/11, p. 5). Bierer called FDP's work "a wonderful effort" and said there were "many areas of overlap" with SACHRP.

"They have the ability to do demonstration projects, and in doing so, they can develop data to show a change in administrative [functions] does not compromise protections," Bierer said. For example, the University of Michigan is experimenting with having IRBs do a continuing review of minimal risk, nonfederal research every two years; the requirement for Public Health Service-funded studies is a year from the first review.

FDP is also developing a "Practical Guide for Reducing Regulatory Burden," which will include a "set of tools that will allow institutions to reduce administrative burdens and maintain superior standards of human subjects protection while adhering to federal regulations," according to the PowerPoint presentation by FDP representatives at the SACHRP meeting. Among the tools in development is an "exemption wizard" that investigators and IRBs would be able to use to help determine whether a project needs IRB review.

According to the presentation, FDP members asked SACHRP to contribute topic ideas for the guide, help critique project materials, clarify guidance, share ideas from SACHRP subcommittees, suggest demonstrations, and volunteer or recommend individuals to serve on FDP's working groups. (A draft of the guide is available at http://hrpp.umich.edu/fdp-hs-burden/index.html.)

"If something like [the exemption wizard] could be developed, it might be a very good tool," Bierer said.

Harmonization Work Reviewed

The final business at the meeting was a review of four projects under way by SACHRP's Subcommittee on Harmonization, which is authorized to meet just three times a year. The subcommittee developed three draft letters and an FAQ-type document.

These are as follows:

◆ ***Planned deviations from protocols.*** Planned protocol deviations are changes that are anticipated to occur, such as when a change is made to accommodate a subject's vacation or to enroll an individual who is slightly older or younger than the age specified in a protocol.

The goal is to "not overload the IRB with trivia," Bierer said. "If you get enough [changes], you can significantly impact the trial" because some may need to go back to the IRB for approval. "That's the tension we need to resolve."

As the draft letter explains, "In the area of human subject protections, there is wide divergence among institutions, sponsors, investigators and IRBs regarding the definition, acceptability, and procedures for reviewing planned protocol deviations. The purpose of this recommendation is to identify various issues relating to planned protocol deviations and to provide HHS with a summary of the issues sufficient to provide consistent direction to the regulated community."

If the draft letter is adopted as written, SACHRP will also recommend that "FDA and OHRP release a joint or a coordinated guidance document providing the regulated community with direction on addressing this issue."

The subcommittee's draft document also points out that "Planned protocol deviations need to be contrasted from...other types of events: 1) deviations from the protocol performed to eliminate apparent immediate hazards to the subject, 2) unplanned deviations from the protocol that are identified before they occur but cannot be prevented, 3) unplanned deviations from the protocol that are discovered after they occur, 4) unanticipated problems, and 5) serious or continuing non-compliance."

◆ ***When research begins.*** Under OHRP-enforced regula-

tions, "research" has not begun when potential research subjects are contacted and screened for possible inclusion in a trial, such as during a short phone call. PHS regulations view such activities permissible — with a waiver of informed consent. But "FDA considers that part of the research protocol" and would require consent and the application of other regulations, Bierer said.

These two are in conflict. One possible resolution, according to the draft recommendation letter, would be for HHS to abandon the waiver requirement. "When researchers intend to obtain informed consent to a study, then their activities incident to obtaining such consent (e.g., identifying and contacting the individuals for consent) should not be regarded as a separate research project requiring a waiver of consent," the draft letter states. "Rather, OHRP should regard this extremely common situation as one overall research project and should not bifurcate it. It should be sufficient for an IRB to review these preparatory activities as an integral part of the overall project, ensure any risks are minimized, and focus on the proposed consent process and documentation. "

In addition, the letter suggests that "OHRP and FDA should take the necessary steps to issue a single joint guidance on recruitment of subjects so that IRBs have a single source of information regarding the agencies' viewpoint on this issue. This will reduce administrative burden on IRBs and ease compliance requirements. SACHRP recommends that OHRP should adopt the FDA approach to this issue, and take steps necessary to interpret the Common Rule so that this is possible."

The draft letter also states, "To the extent possible, the Office for Civil Rights should also consider what activities must be performed due to HIPAA/HITECH," the two laws governing the privacy and security of medical information.

"We want to align the guidance because the same studies are often co-regulated" by FDA and HHS, Bierer said.

◆ ***The use of deception in research.*** At its last meeting, SACHRP discussed the purposeful use of deception in research (*RRC* 11/10, p. 4). Its harmonization subgroup prepared a letter that was reviewed by SACHRP and will be finalized at its next meeting.

In the draft letter, SACHRP recommends that OHRP "issue guidance regarding the acceptability of the use of deception in research regulated by HHS. The guidance should inform institutions, investigators and IRBs of OHRP's expectations regarding the application of the IRB and informed consent regulations to the use of deception in research." The draft letter notes that "Deception is frequently used in psychology, neuroscience, behavioral, and economic research, and is occasionally used in clinical research."

The draft letter also addresses what the guidance should contain, including clarification that "deception should not be used when non-deceptive alternatives are available and should not be used unless the research has sufficient potential social value to justify the risks associated with deception" and that "risks of the use of deception include psychological distress or harm, and mistrust in the enterprise of research."

◆ ***Applicability of FDA regulations.*** The subcommittee also made progress on a document that requests FDA make clear, through examples, the kinds of research that falls under its regulations. "For the vast majority of clinical investigations regulated by FDA, the determination of whether the study is regulated is easy to make and clear," the draft document states. "Phase 1, 2, and 3 clinical trials are clinical investigations. But not all clinical investigations are clinical trials. There are several areas of research or investigation involving humans where the determination of whether the FDA regulations apply is not clear."

The document outlines "seven areas where an investigation might meet the definition of a clinical investigation subject to FDA regulation," of which four refer to the use of specific methods; the last three relate to specific activities involving a test article.

Examples cited include record reviews, the collection and analysis of data that occur as part of medical care, and the use of tissue banks and registries.

New Members Must Be Named

SACHRP's next meeting is July 19–20. At that time, the three subcommittee letters and FAQ document are expected to be reviewed again and approved.

In addition, SACHRP should have four new members, to replace the following whose four-year terms will have expired by then: Elizabeth Bankert, assistant provost and human subject protection official at Dartmouth College; Lisa Leiden, senior director of research for the Office of Research Administration for Seaton Family of Hospitals; Patricia Marshall, professor of bioethics and anthropology in the Department of Bioethics at Case Western Reserve University; and David Strauss, M.D., deputy director for research at New York State Psychiatric Institute and vice chairman of research administration, ethics and policy in the Department of Psychiatry at Columbia University College of Physicians and Surgeons.

Link: www.hhs.gov/ohrp/sachrp/mtgings/mtg03-11/sachrp_mtg_march2011.html. ✧