

# CLINICAL TRIALS

## *Advisor*<sup>®</sup>

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## Legislation

### Lawmakers Focus Increased Attention On Human Subject Protection Changes

Congress seems poised to make major revisions to current human subject protection (HSP) rules, and sites and IRBs should pay close attention to what lawmakers have in mind, say Capitol Hill insiders and industry experts.

The U.S. House of Representatives is expected to take a close look at the Human Subjects Protections Act of 2002 (HR 4647), which embodies all of the major changes recommended by the Office of Inspector General (OIG) in 1998.

The major intent of the bill is to dramatically increase federal oversight and enforcement in HSP, a congressional aide tells *CTA*. The measure also boosts the budget for the Office of Human Research Protections (OHRP), from \$8 million to \$20 million, beginning FY 2003 (October 2002). The additional funds are earmarked specifically for enhanced enforcement efforts.

Reps. Diana DeGette (D-CO) and James Greenwood (R-PA) introduced HR 4647 May 9. Greenwood chairs the House Committee on Energy and Commerce Subcommittee on Oversight and Investigations, which is expected to hold hearings on the measure in July.

Industry experts are taking the latest Congressional efforts on HSP very seriously. "IRBs are going to undergo a sea change in the next five years," predicts Felix Gyi, PharmD, MBA, president and CEO of Chesapeake Research Review Inc., in Columbia,

MD. If HR 4647 becomes law, it will have a "huge impact," asserts Daniel Nelson, MS, CIP, associate professor and director of the Office of Human Research Studies at the University of North Carolina-Chapel Hill, and current president of Applied Research Ethics National Association (ARENA). The proposed changes are positive attempts to improve human subject protection in the long-term, but they also create new, short-term workload burdens for IRBs, according to Nelson and Gyi.

Alan Milstein, an attorney who has brought several lawsuits against research sites and IRBs in the last year, comes at the legislation from a different perspective: "I don't see the point of this legislation without a clause that gives a person a private right of action. If a subject is harmed, he should be allowed to bring a claim in federal court for damages and attorney fees." But Milstein is behind the increased emphasis on federal enforcement of regulations. "The only thing that will create change is to put real teeth in this bill. If the purpose of the bill is to prevent death, I don't think this does it, however," he tells *CTA*.

#### 10 Key Provisions

The measure contains 10 key provisions for sites and IRBs:

**1. Harmonization of existing federal regulations on human subject protection:** The Secretary of the Department of Health and Human

Services (HHS) would be required to complete a review of subpart A of 45 CFR 46 (HHS regulations) and 21 CFR 50 and 56 (FDA regulations) to determine where harmonization was possible and to recommend changes within 18 months of passage. The bill specifically requires HHS to publish a proposed rule to modify the current regulations in this area within three years. Any rule promulgated by HHS in the interim that would result in differences with FDA regulations would then have to include an explanation for the variation.

**2. IRB membership requirements:** To establish quorums, IRBs would be required to have present no fewer than two members or 25 percent of all members, whichever is greater, whose primary expertise is scientific; two members or 20 percent, whose primary expertise is non-scientific; and two members or 20 percent, who are non-affiliated with the institution represented by the IRB. One person could qualify as both non-affiliated and a non-scientist. A non-affiliated member cannot be an immediate family member of someone who is affiliated.

"This may have a bigger impact on academic medical centers that have larger IRBs with more members," says Gyi. "This may create difficulties for some IRBs, but it is in keeping with the spirit of current regulations," adds Nelson. "Some IRBs have up to 20-30 members to provide the necessary expertise. In this situation, if you have only one token non-scientist or non-affiliated member as the current regulations require, sometimes represented in a single person, the danger is that important voice gets lost," Nelson says. "Requiring some percentage of the membership from these groups takes us back to the original intent of a diverse, independent group," he explains. "But it is becoming harder to recruit and keep IRB members now and this will make it even more difficult," he says.

In addition, the bill requires that, when reviewing protocols involving vulnerable subjects, the IRBs have "at least one member who is an expert in the issues involving such population," and that member must have full voting rights. Likewise, when reviewing protocols involving "a significant number of minority individuals," the IRB must include minority members with full voting rights. But, the bottom line in this area, according to Gyi, is the culture involving IRBs: "IRBs should move to a culture of trust and conversation, and members should have the moral courage to stand up for what is right."

**3. Informed consent:** The bill establishes a legal right to informed consent for trial participants and details eight essential elements:

- ◆ Purpose of the research;
- ◆ Potential risks and benefits;
- ◆ Differences between research and available therapeutic treatment;
- ◆ Right to withdraw;
- ◆ Identity of the sponsor;
- ◆ Any conflict of interest for investigators;
- ◆ Medical tests and procedures necessary for participation and the extent to which these tests and procedures will not be paid by the sponsor or site; and
- ◆ "Such additional information as HHS may require."

**4. Administrative requirements:** The bill establishes the authority of HHS to modify the Common Rule on vulnerable populations. "All research protections will come under the Common Rule," explains Dawn Jackson, legislative aide to DeGette. "Congress' intent is to create a floor of protection. Agency heads can go above this floor," she

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tells **CTA**. The bill allows HHS to change the Common Rule without the signatures of all agency heads that fall under it, Jackson explains.

The bill also requires investigators to file written attestations to comply with HSP regulations, to disclose any conflicts of interest (including non-proprietary interests) to IRBs and to inform an IRB when the proposed protocol has been submitted to any other IRBs.

IRB members also must disclose conflicts of interest and cannot review protocols in which they have any interest. Finally, institutions must provide annual reports to the government on the numbers of new and continuing protocols reviewed and number of subjects enrolled in trials.

**5. Multicenter trials:** The proposed changes would permit review by a “lead IRB” as an option for multicenter trials. “Information-sharing among IRBs is often overlooked, especially in multicenter trials,” says Nelson. “Anything that promotes this would be positive both in sharing the fruits of review and any negative information,” he asserts. Nelson says there already are mechanisms to allow cooperative review in a multicenter trials, but few sites take advantage of them.

**6. Data safety monitoring committees:** The bill would require DSMBs for certain high risk trials and mandate that DSMBs provide summary information to IRBs. IRBs must consider the proposed monitoring plan before approving high risk trials. “IRBs are poorly positioned to function as DSMBs,” says Nelson, “and it can only improve the process to

both have DSMBs in place and ensure that they communicate with IRBs.”

**7. Education and accreditation:** Institutions must provide education and training in HSP for investigators and IRB members and continuing education for IRB members. The bill permits HHS to make grants for the development of a “model education program” for HSP best practices and also allows institutions to recover the cost from federally funded trials as direct costs.

Accreditation of HSP programs would be voluntary, and accrediting bodies would be evaluated and “recognized” by HHS.

**8. Adverse event reporting:** The bill requires investigators to report all AEs to IRBs, sponsors and either OHRP or FDA.

**9. Wider enforcement options:** Under the bill, there are several ways for OHRP to enforce compliance:

Suspending protocols;

- ◆ Prohibiting new subject enrollment;
- ◆ Suspending or terminating a particular research project;
- ◆ Suspending federal funds for particular research protocols;
- ◆ Suspending all research projects; and
- ◆ Suspending or debarring investigators.

**10. Additional grant funding:** The bill permits grants for the purpose of assisting institutions in “carrying out programs to recruit and train minority individuals to serve as IRB members.”

## Compliance

### OHRP Letters Address Multicenter Trials Issues

*Warning to sites:* OHRP is concentrating on multicenter trials — as evidenced by several compliance letters sent out by the agency last month.

Specifically, several sites involved in a trial involving estrogen replacement therapy for treatment of mild to moderate Alzheimer’s Disease received letters about recurring issues involving informed consent and the participation of a caregiver in the trial.

In that trial, the consent documents failed to include a description of the procedure for having the subject’s caregiver accompany the subject to all clinic visits and administer the study drug, according to OHRP. Sites

also failed to ask the caregiver to complete quality of life and pharmacoeconomic questionnaires related to the subject’s condition and care, the agency asserted.

“If a subject’s participation is contingent upon another person’s involvement in the research procedure, a statement must be included to inform the subject regarding what will be expected of the other participant,” OHRP stated.

The agency also noted that the consent documents did not describe alternatives for receiving estrogen therapy outside the context of the research study. The sites noted that the use of ERT was not approved

specifically to treat Alzheimer's Disease. But OHRP pointed out that subjects should have been told that they could receive ERT—without enrolling in the study—for other common indications, such as osteoporosis, menopausal vasomotor symptoms and atrophic vaginitis. "When a particular marketed drug is being used by health care providers to treat patients for an indication which has not been approved by FDA, it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document," OHRP concluded.

OHRP also said that one site failed to conduct continuing review on an annual basis, failed to report the first three serious adverse events in the trial to the IRB and "one neurologist consented a subject prior to approval of an amendment adding him as a co-investigator."

In a compliance letter to Cornell Medical Center, OHRP cited problems in several cystic fibrosis trials using adenovirus vector. OHRP said Cornell failed to report unanticipated problems involving risk to the IRB and OHRP, deviated from the protocol by administering the wrong adenovirus vector dose to one patient and listed an "unexpected complication" in its continuing review report without notifying OHRP.

### Consent Violations

Numerous violations in the consent documents were cited, including:

- ◆ Lacking a statement that the study involved research;
- ◆ Not including an explanation of the purposes of the research;
- ◆ Not fully describing the study procedures and identifying these procedures as experimental;
- ◆ Not describing reasonably foreseeable risks and discomforts of the procedure, such as a skin biopsy, mild liver inflammation and cardiac arrhythmia; and

- ◆ Not describing previous adverse events reported to FDA.

OHRP also said that consent documents overstated benefits by referring to the research as "treatment for cystic fibrosis." It also charged that Cornell's IRB used expedited review inconsistent with regulations: "The continuing review of the protocol was conducted in an expedited manner, but three subjects had been accrued since the last continuing review." Finally, the agency stated: "Continuing review of the protocol was conducted in an expedited manner, although subjects enrolled since the last review and subjects were still being followed up. The follow-up in the protocols appears to have included research-related interventions (e.g. bronchoscopies) and therefore expedited continuing review would not seem to have been appropriate."

Overall, however, OHRP said it was pleased that Cornell had taken "numerous corrective actions to address these findings." ◆

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## In Brief

**HII Creates HSP Award:** Health Improvement Institute (HII), a private, not for profit corporation based in Bethesda, MD, is formulating criteria for a new national "Award for Excellence in Human Research Protection."

HII is developing this awards program under a contract from the Department of Health and Human Services' Office for Human Research Protections. Under the program, an independent, non-governmental board will select awardees to recognize excellence in their programs for protection of human research participants.

To learn more about the awards program, download participation forms from the program website at <http://www.hii.org>, or send an e-mail to [hii@mcman.com](mailto:hii@mcman.com).

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