US research safety system 'in jeopardy'

[WASHINGTON] The effectiveness of institutional review boards (IRBs), the linchpin of the US system for monitoring the safety of human experimental subjects, is "in jeopardy", according to the Department of Health and Human Services (DHHS). A burgeoning workload has led to hurried, uninformed reviews with inadequate follow-up, its inspector general claims.

A four-volume report, released at a Congressional hearing last week, says changes in the research environment since IRBs were instituted 25 years ago have led to a system of boards that are incapable of fulfilling their role in the expanding world of US research.

"We are offering a very loud warning signal," said George Grob, the deputy inspector general for evaluation and inspections, who testified at the hearing on behalf of the inspector general. "We are saying major change needs to be made."

But Gary Ellis, director of the Office for Protection from Research Risks (OPRR) at the National Institutes of Health, said the risk of "catastrophic" failure of the current system was slight. He added: "One thing IRBs are not in is jeopardy. Let us set aside any sense of peril, danger, hazard or menace."

IRBs review the ethics of federally funded experiments involving human subjects, as well as studies on drugs and medical devices that must be approved by the Food and Drug Administration (FDA). The report claims their independence is threatened by an expectation that they should support their institution's interests — raising money and prestige by encouraging clinical research — as well as protect human subjects.

The report says IRBs offer their members little education on government ethics rules,

conduct minimal review of research that has already been approved, and review first-time proposals hastily. "They review too much, too quickly, with too little expertise," it says.

Among its recommendations are that IRBs should be relieved of perfunctory, procedural requirements that bog them down, and should include more non-scientific and non-institutional members.

At the root of the current predicament, it says, is the extra workload created by fundamental changes in the structure of research, including a proliferation of multi-site trials and an increasing number of research proposals — which will grow further if generous funding increases for the NIH continue.

Grob said the IRB system was built for a system that largely did not exist any more, comparing it to a shield that was "brittle, strained and… even cracked".

Christopher Shays (Republican, Connecticut), who chaired the hearing as head of the human resources subcommittee of the House Government Reform and Oversight Committee, said the report, if anything, understates Congressional concerns that IRBs are "in jeopardy of being overwhelmed by the weight and complexity of their work".

For instance, he said the system "failed miserably" in a recent New York case in which healthy black and Latino boys, the younger brothers of delinquents, were given the now-banned drug fenfluramine to study their aggressive tendencies (see box). Yet even Shays, a leading critic of IRBs, did not suggest Congress should intervene by writing new laws. Many necessary reforms, he said, were within the power of IRB sponsors and administrators to implement at once.

Grob pointed to increased commercial sponsorship: "IRBs feel pressure to accommodate these sponsors who are looking for quick turnaround of their research and for whom time is money," he said.

Speaking on behalf of the Association of American Medical Colleges, Robert Levine, a professor of medicine at Yale University, called it "most unfortunate" that the tone of the report — which did not catalogue specific ethical lapses and specifically said it claims no widespread abuses of research subjects — "conflicts with its substance". It seemed to portray a system in crisis yet yielded no evidence of harm, Levine said, warning that adverse publicity would make it even harder to recruit high-quality people for demanding, largely unpaid IRB work.

Bert Spilker, the senior vice-president for scientific and regulatory affairs at the Pharmaceutical Research and Manufacturers of America, declared the IRB system "sound" and "working well". He urged the adoption of modest reforms to improve IRBs' efficiency but without new laws. He challenged a recommendation in the report that IRBs monitor clinical trials in progress, saying it was not necessary or appropriate because either drug companies audit the trials themselves or hire others to do this, or the FDA audits them.

Spilker said the notion that IRBs face conflict because of allegiance to their institutions was more theoretical than real. Levine said it was not in the interests of institutions to have their IRBs approving experiments that led to bad press or lawsuits.

Shays called it "pathetic" that the OPRR, which is charged with ensuring the protection of human subjects in all research conducted or funded by the DHHS, has only one full-time investigative worker.

Among its 70 current investigations, the OPRR carried out only one on-site investigation in the past year, Ellis said. That, at the University of Maryland, found that the IRB was understaffed, undereducated and has been meeting and approving experiments without a quorum. **Meredith Wadman**

Review board head defends fenfluramine tests

[WASHINGTON] B. Timothy Walsh, a chair of the IRB that approved experiments in which fenfluramine, a now-banned diet drug, was given to healthy boys from ethnic minorities, defended his panel's decision last week before a Congressional hearing examining IRB effectiveness (see *Nature* **392,** 747; 1998 & **393,** 406; 1998.)

Walsh, who co-chaired the IRB at the New York Psychiatric Institute in Manhattan, told the human resources subcommittee of the House Government Reform and Oversight Committee that his IRB concluded that a single, oral dose of fenfluramine presented risks that were "minor at most".

There was "no indication", he said, that a single dose of the drug causes heart valve damage like that seen in adults who took it for months, prompting its recall in 1997, two years after the New York experiment was stopped.

He added that the study of aggression risks in the boys, aged six to ten years old, was a type of research "critical for our country".

But Congressman Edolphus Towns (Democrat, New York) called the IRB's approval of the experiment "very, very troubling". He produced an early proposal from the investigators in which white children were excluded; Walsh said the IRB required the investigators to change it to include all races.

Despite this, Towns complained, all of the study participants were black or Latino. "These children were chosen by design, not by chance," he said. "If this case is indicative, the IRB process... needs to be torn down and rebuilt from scratch, not reformed." **M.W.**