Affirmative Action for Clinical Trials

Congress is about to pass a bill that will require the National Institutes of Health (NIH) to include substantial numbers of women and members of minority groups in clinical trials. The provision, championed by the Congressional Caucus for Women's Issues, may not seem like a radical idea at a time when NIH itself is paying increased attention to the health problems of women (see main text). But it has sparked a rash of protests from researchers who fear that it could add to the cost and complexity of clinical research, and it has drawn some sharp barbs from NIH Director Bernadine Healy, who has accused Congress of meddling in the conduct of health research.

The offending language is included in separate versions of the NIH reauthorization bill passed by both the House and the Senate. It is almost certain to be included in the final version, which Congress is expected to approve in the next few weeks. The provision directs NIH to design clinical trials so that "a valid analysis" will show whether treatments "affect women or members of minority groups...differently than [sic] other subjects in the trial." The bill doesn't define "valid analysis," but the term "implies having [data of] equal precision" for many different subgroups, says Curtis Meinert, a biostatistician at the Johns Hopkins School of Hygiene and Public Health who designs clinical trials. "That means you have to double, triple, or quadruple sample size," he says.

There are some loopholes. Trial designers can ignore the inclusion rule if they have "substantial scientific data" showing the treatment does not affect women and minorities differently, or if there is reason to believe that expanding the enrollment would jeopardize patients' health or the purposes of the trial. And the NIH director is given leeway to decide when "other circumstances" require the rule to be suspended.

These loopholes were added after earlier versions of the legislation, which were even more strict, ran into a barrage of complaints. But researchers are not entirely mollified because they believe the legislation could still lead to some trials that are broader than needed. "Where [gender analysis] is relevant, it should be incorporated—I've been an advocate of that," says Nancy Sambol, a pharmacologist at the University of California, San Francisco. But "to do it across the board is very much overkill. You don't want to overregulate and study things just to study them."

Healy is not entirely happy either. Last May, she upset the Congressional Caucus for Women's Issues by sending a letter to her boss, Secretary of Health and Human Services Louis Sullivan, complaining that the legislation contained "highly intrusive language" that "micromanages some of NIH's important research programs." Although some of the provisions Healy disliked in that version have been modified, she still objects to Congress intruding into the design of research protocols. "If they want to do science, let them enroll in the executive branch and come over here and work at NIH," Healy told *Science* last week. Representative Pat Schroeder (D–CO), cochair of the Women's Caucus, is unmoved. "The law will make the policy permanent and will ensure that biomedical research does not once again overlook women and their health," she says.

–Traci Watson

Walter Willett, a Harvard epidemiologist and a skeptic, says: "I don't know of anyone who is not involved in the study who thinks that it will provide a decisive answer" on the low-fat hypothesis. His own research on a group of more than 100,000 nurses has found no evidence to support the theory. Willett is not alone. Several other epidemiologists—including Rosenberg, Bush, and Petitti—worry that this trial has some similarities to an NIH-funded study, focused exclusively on men, that ended in the early 1980s without answering the questions it tackled. Known as MRFIT (for Multiple Risk Factor Intervention Trials), it sought to decrease heart disease by getting subjects to adopt a low-fat diet and make other "lifestyle" changes. Because subjects were asked to change several habits at once, says Willett, it was hard to link causes with the effects that were observed. The same could happen with the WHI trial, Willett warns, because it also will ask participants to lower fat intake while increasing fiber and vitamin A in foods.

Healy responds that the women's health trial "is a much better study than MRFIT" because it will have a well-controlled placebo group and other statistical controls to permit a more sophisticated analysis of the results. Maureen Henderson, principal investigator at the WHI clinic in Seattle and a veteran of the diet debates, agrees that if there is a link between lowered fat intake and decreased risk of cancer, this study will be likely to pick it up. But she adds that the overall rationale for the multipronged trial does not rest on "whether or not one of the results is positive." It may reveal the interactive effects of hormone use and dieting, for example, and provide data for all kinds of undreamed-of research projects.

When to stop?

The trial of hormone therapies has come in for much less criticism than the low-fat diet study, in part because cause and effect is likely to be easier to pin down. Indeed, early evidence of estrogen's usefulness presents a dilemma that came up at last week's advisory committee: What would happen if it becomes clear after only a few years that women on estrogen are getting significantly fewer bone fractures? Many researchers expect this will happen. Will NIH stop the trial and break up the placebo group, even though it might mean losing a chance to answer the bigger questions about estrogen's effects on heart disease and cancer?

Rossouw says these issues will be dealt with by a design monitoring and safety board, not yet empaneled. It will meet for the first time next month and establish guidelines as it sees fit. He hopes that in considering ethical issues the group will not focus on narrow endpoints—such as the frequency of fractures—but look instead at the volunteers' overall quality of life and total mortality. Indeed, that is exactly what the principal investigators want to do, says cardiologist Philip Greenland, who directs the WHI clinic based at Northwestern University. "We are breaking new ground," Greenland says, in asking the monitoring board to consider net benefit in deciding whether or not to let the trial go forward. No other major trial has done that. Deciding when to call a halt to trials with multiple objectives is always "a knotty question," Greenland adds. But if NIH uses the proposed broad approach, it should be possible to continue the trial long enough to get adequate data on heart disease as well as osteoporosis. That sounds fine, the skeptics say, as long as volunteers are fully informed of the risks.

And the risks may well be worth taking, says advisory panel member Phyllis Leppert, chief of obstetrics at the Rochester General Hospital in Rochester, New York. Why? Because the results could have an immediate value in guiding medical practice. This study, Leppert says, is really getting started about "20 years late." Hormone replacement therapy is already growing by leaps and bounds, but without much experimental evidence to guide it. Some surveys indicate that about 10% to 15% of women in this age group are being prescribed estrogen or estrogen plus progestin. If the study is allowed to run to completion, doctors will finally learn whether the hormones they prescribe (or avoid) are as beneficial (or as detrimental) as they believe.

A billion-dollar project?

Even if the study does answer some of these questions, the critics keep coming back to the bottom line: Is it worth the price? And already, NIH is beginning to have trouble