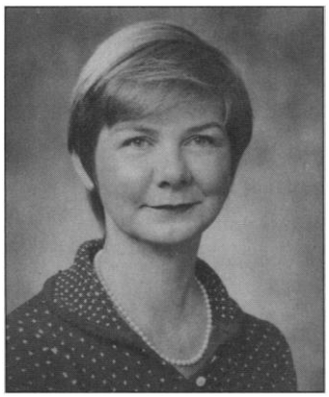
NATIONAL INSTITUTES OF HEALTH

New Law Brings Affirmative Action to Clinical Research

If you have a grant application for a Phase III clinical trial awaiting approval by the National Institutes of Health (NIH), you may be in for a surprise. NIH is now reviewing your application to make sure that it conforms to new guidelines—guidelines that haven't even been published yet—on the inclusion of women and minority groups* in clinical studies. These guidelines are the result of a law, lobbied through Congress by advocates of women's health programs, meant to guarantee that there will be no more trials involving only white males—as happened, for example, in a 1980s study of aspirin and heart attacks—unless such exclusivity is based on good science. The law also aims to get researchers to look for biological differences between white males, women, and nonwhites.



Good science. Extramural chief Wendy Baldwin says new rules won't undermine quality.

These may be reasonable objectives, but the idea of Congress mandating the design of clinical research has triggered a deluge of criticism from scientists leery of "politically correct clinical trials"—in the phrase of independent biostatistician Janet Wittes, formerly of the National Heart, Lung, and Blood Institute. And some researchers who have seen the outline of the new rules complain that they could greatly increase the cost of some studies for little scientific return.

The gender/ethnic policy is part of the reauthorization bill for NIH, signed into law last June. Since then, says NIH extramural research chief Wendy Baldwin, NIH staffers have been "working feverishly," to write guidelines telling grant applicants how to meet the law's requirements. They completed their work in December, but the new rules won't be published until they've been approved by the Department of Health and Human Services and the Office of Management and Budget. Meanwhile, to bring all new projects into compliance quickly, NIH is applying the guidelines retroactively to 10 June 1993. NIH is trying to let researchers know what to expect, and Baldwin began briefing small groups last week on the rules' impact.

Many researchers will be relieved that NIH is not reading the law literally. The law says that "any clinical trial" funded by NIH and not ruled exempt by the director of NIH must "provide for a valid analysis" of gender and racial differences. The law lifts this requirement when imposing it would be "inappropriate" for the health of the subjects, for the purposes of the research, or for other reasons cited by the director of NIH. However, according to a policy statement released by Baldwin, the new guidelines will apply only to the final stage of research—the Phase III trials that typically include thousands of subjects. And not all of these will have to collect enough data to yield statistically significant results in every category.

Most studies will fall into one of three groupings. First are those for which strong prior evidence indicates that the results will not show gender or racial differences. These studies will not be required to recruit a diverse test population. Second are those for which there is strong evidence to expect gender or racial differences—perhaps affecting antihypertensive or diabetes drug research. These trials must be designed to obtain significant results for groups in which a different response is expected. Third is a large, gray area likely to include most trials—those for which the available evidence points neither one way or the other. These will have to "include sufficient and appropriate entry of gender and racial/ethnic subgroups, so that valid analysis of the intervention effect in subgroups can be performed." NIH has decided, however, that such studies need not "provide high statistical power for each subgroup."

"You've got to ferret out the data wherever you can find it," says Judith LaRosa of the NIH office of research on women's health. One important impact of the guidelines, predicts LaRosa, will be to require clinics to form partnerships to achieve overall racial and gender balance. She's preparing an "outreach notebook" to be sent to NIH grantees with tips on how to do this. Meanwhile, she's reviewing "over 50" clinical trials that are awaiting funding to see whether they need to be modified to meet the new requirements. Applicants seeking 1995 funds for Phase III trials must prepare applications telling how the study design will comply with the new guidelines.

The response to NIH's effort to comply with the law has been mixed. Biostatisticians who didn't like the mandate to begin with are, predictably, still unhappy. One distinguished clinician—Lewis Kuller of the University of Pittsburgh—thinks the government is leaning toward a "racist approach to medicine" that could undermine the integrity of research. Paul Meier, a statistician at Columbia University, says he supports the goal of broad inclusivity, but the idea of routinely searching for biological differences between whites and all other racial groups is "not in the public interest."

In fact, argue Meier and Curtis Meinert, a biostatistician at Johns Hopkins University, the new requirements could sharply reduce the amount of research that can be done for a given amount of money, by requiring a four- to tenfold increase in the number of people enrolled in some trials. And they object that there's no scientific basis for mandating interracial comparisons. They say they know of no evidence—other than from studies of obvious genetic abnormalities—suggesting that medical interventions that are good for one ethnic group are harmful for another. Meier argues that even if NIH has come up with a benign interpretation of a bad law, "we should still argue the matter." Scientists shouldn't just say, "Yes, Poppa."

Yet those who are enthusiastic about the new policy—including Florence Haseltine, director of the center for population research at the National Institute of Child Health and Human Development—say it's long overdue. It shouldn't take a government order to get researchers to include women and minorities in big trials, she says, but it wasn't happening otherwise. Of particular concern, says Kay Dickersin, a clinical trials expert at the University of Maryland, is the possibility that women may respond to drugs differently from men because they are exposed to different natural and synthetic hormones. "How can we know there are no differences until we've done the studies?" she asks.

Mary Foulkes, an AIDS trials expert at the National Institute of Allergy and Infectious Diseases, acknowledges that "change is painful," but, she adds, "in the long run, this one will be good for everyone." And Baldwin suggests that the complaints may be coming from people who don't realize that NIH intends to uphold "good science." NIH Director Harold Varmus adds that while "we at NIH will make every effort to help applicants conform to the spirit" of the law, "we do not intend to make these guidelines barriers to research."

–Eliot Marshall

*The official minority groups are Asian/Pacific Islander, black, Hispanic, and Native American, but NIH says researchers may use other subcategories if study participants want to be classified differently.