NIH Unveils Plan for Women's Health Project

Is an epidemiological survey and a set of clinical trials involving 140,000 postmenopausal women too ambitious?

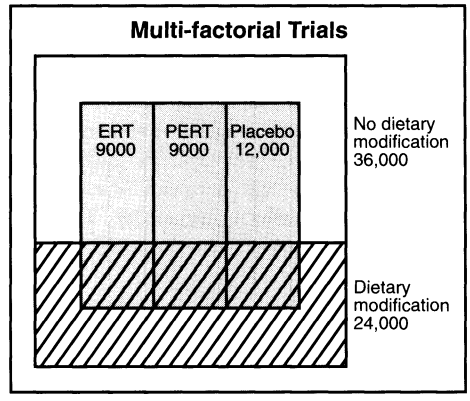
IMAGINE YOU HAVE 9 MONTHS TO PLAN A 10-year, $500-million study involving more than 140,000 subjects—the largest single research project ever launched by the National Institutes of Health (NIH). And even before you come up with a preliminary plan, the whole notion of the project has come under attack from some researchers who argue that it could end up being a monumental waste of money. That's the uncomfortable position William R. Harlan now finds himself in as director of NIH's giant Women's Health Initiative.

Harlan, head of NIH's Office of Disease Prevention, has until the beginning of next year to put out the requests for contracts that will actually get the project under way. Last week he and his NIH colleagues unveiled their latest plans for the initiative at a day-and-a-half-long public meeting, and they got a chance to hear firsthand just what their critics were saying.

The initiative is the brainchild of NIH director Bernadine Healy. Within a week of her confirmation as director last April, Healy announced that she had a dramatic plan to redress what she called the years of neglect of women's health issues. She proposed a three-part study of postmenopausal women: one part would involve some 70,000 women in a set of clinical trials to measure the effectiveness of hormone replacement therapy, dietary modification, and vitamin supplements to combat heart disease, cancer, and osteoporosis; a second would seek effective ways to promote healthy behavior within local communities; and a third would be an observational study involving a minimum of 70,000 women over age 50 who would be screened for signs of progressive diseases and predictors of future illnesses.

But from the first there were skeptics. Why, many advocacy groups wanted to know, were women of reproductive age being excluded from the study? What exactly would be learned from this giant project that couldn't be learned from smaller, less expensive studies? And why was NIH proposing a large, centrally administered project instead of the more common investigator-initiated approach?

Harlan has considered these criticisms and is not fazed by them. He argues that a study involving women of all ages would be prohibitively expensive, and that focusing on postmenopausal women is appropriate because it serves two relatively neglected populations—older persons and women—at the same time. He says a large, centralized study is essential to be certain that, if the therapies really do have a beneficial effect, researchers will have the statistical power to see these effects in a mass of data.



Multiplier. *Overlap between dietary studies and trials of estrogen replacement therapy (ERT) and progestin-estrogen replacement therapy (PERT) should reveal any additive effects of different regimens.*

But at last week's meeting, Harlan heard some more specific objections to the proposed clinical trials—the centerpiece of the study. There are three different trials being planned: one would compare estrogen replacement therapy with estrogen therapy plus progesterone as a method to reduce heart disease and bone loss; a second would look at the effectiveness of a low-fat diet to prevent breast cancer; and a third would test vitamin D and calcium supplements to prevent bone loss and reduce colon cancer. NIH intends to run the three trials concurrently, with some subjects participating in all of them. The advantage of such a factorial design is that the results should shed light on any interactions between the three interventions. For example, if hormones and vitamins individually reduced the risk of bone loss, but together increased the risk of cancer, that should show up in the results.

But, in spite of this advantage, the factorial design of the project could be its Achilles' heel, says Lynn Rosenberg, professor of epidemiology at Boston University School of Public Health and president-elect of the Society for Epidemiologic Research. On 17 July Rosenberg and 41 female colleagues laid out their concerns about the initiative in a letter to Healy, and last week Rosenberg elaborated on those objections. She says it's always a challenge to get subjects to adhere strictly to trial protocols, and many women will certainly drop out of the hormone replacement study because there are unpleasant side effects from the drugs, such as bleeding and depression. To expect thousands of women to stay on hormone replacement, modify their diet, and take vitamin supplements all at the same time, and to do so religiously over a 10-year period, is not realistic, she says.

Rosenberg also argues that NIH may have chosen the wrong interventions to study. While she agrees the time is probably right to begin a trial of hormone replacement therapy, Rosenberg questions whether there's enough evidence to start a large diet modification trial. She also points out that it will be difficult to be certain that the planned diet intervention is working, since subjects will also be put on an exercise regimen. Why not, asks Rosenberg, simply do a trial of moderate exercise, a far easier lifestyle change to accomplish?

Trudy L. Bush, an epidemiologist at the Johns Hopkins University in Baltimore, is also troubled by the complexity of the proposed initiative. She is an investigator in the smaller NIH-sponsored Postmenopausal Estrogen and Progestin Interventions Trial, which looks at many of the same issues that the Women's Health Initiative trial will. "I and many other practicing epidemiologists believe that [the Women's Health Initiative] is too complex to succeed as currently designed," she told NIH officials at last week's meeting. Bush argues that multiple interventions should be undertaken only when the interventions are simple or when the trial is short term.

Harlan readily acknowledges that the complexity of the trial is staggering, and he hints that the calcium/vitamin D arm may be dropped from the factorial design. But he argues that the project is feasible. He is also sensitive to the charge that he and NIH are trying to do too much too soon, but he insists that the study can and will proceed even while the design is being modified.

Congress evidently agrees: Last week a House-Senate conference on NIH's budget agreed to give $25 million for the current fiscal year to launch the project. Harlan says the project will gel only when the contract proposals come in and it becomes clear what researchers think it is feasible. "I'm not sure exactly where we're going," says Harlan, "but we're getting there fast." ■ JOSEPH PALCA