Big Science Enters the Clinic

The Women's Health Initiative has an ambitious goal: to assess major risk factors affecting the health of older women. But critics charge that it may be too ambitious

This September, 16 medical centers around the country will embark on one of the largest clinical research projects ever undertaken in the United States. By next year, the effort may encompass 45 centers, in a massive undertaking costing more than $600 million. This is getting close to the lower limits of Big Science, but what really sets it apart is its focus: women's health. Known as the Women's Health Initiative (WHI), the project is an extraordinary venture launched in 1991 by the director of the National Institutes of Health (NIH), Bernadine Healy, with strong backing from Congress.

RICK KOZAK

Money matters. Bernadine Healy says the dispute is more about distribution of funds than science.

The centerpiece of the initiative is a gargantuan clinical trial involving 57,000 postmenopausal women who will be recruited to test the effects of low-fat diets, hormone therapy, and vitamin D and calcium supplements on heart disease, cancer, and osteoporosis. Some will be given just one therapy, others a combination of two or all three, in an intricately overlapping set of studies designed to wring as much information as possible from the test subjects (see p. 745). And that's not all: An additional 100,000 women will be enrolled in an observational study designed to collect baseline data that may help identify valuable markers of disease in the future, and a third effort will test preventive health education programs in 16 target communities. The overall project is so large and so complex, Healy says, it will be "almost like a military campaign."

But if this project is characterized by its high ambition, it is also characterized, as are so many other Healy ventures, by its high controversy. Just last week, Healy, WHI project director William Harlan, and the clinical trial's program officer, Jacques Rossouw, received a somewhat chilly reception when they outlined the project at the first-ever meeting of the initiative's advisory board—a diverse body that includes social scientists, surgeons, and epidemiologists, together with nonscientists such as Olympic athlete Jackie Joyner-Kersee (absent that day), author Gail Sheehy, and columnist Judith Martin. The group listened politely in the morning, but after lunch they tore up the script for the afternoon, peppering NIH officials with questions about the hypotheses to be tested, ethical issues, the trial's cost, and how the whole enterprise would be managed.

It was not the first time the effort has come under fire. Several of the nation's top female epidemiologists—including Lynn Rosenberg of Boston University and Trudy Bush of Johns Hopkins, to name two—criticized the project publicly in 1991, during the only other public review of its design to date, calling it a grandiose effort that may not produce clear-cut results. In connection with that review, 42 women scientists sent a letter to Healy, warning of serious flaws in the study. They argued that some parts of the clinical trial—the hormone therapy studies, in particular—may be valuable, but they questioned whether the low-fat diet study was worth doing. They took issue in particular with the whole notion of conducting a massive, intertwined set of clinical trials, arguing that more focused individual trials might produce useful results more cheaply. (The observational study and the community health project have, in contrast, raised little controversy.)

To Healy, much of the carping is not so much a scientific dispute as a fight over the distribution of NIH's funds. Some scientists are simply raising the "old saw" that individual researchers working on small projects do better science than NIH can produce with huge contract projects like this one, Healy said in an interview with *Science*. These are "concerns that are raised every time we do a study."

Central management

In one sense, Healy is correct: The debate over the initiative is, indeed, a debate over the management of big science. In this case, the critics are not just focusing on the cost and design of the clinical trials, but they are also contending that the project has, to use Healy's metaphor, been conceived and planned like a military campaign—from the top down, without enough input from the research community, they claim.

THE VANGUARD CENTERS

Principal Investigator	Institution
William B. Applegate	University of Tennessee Department of Preventive Medicine, Memphis, TN
Annlouise R. Assaf	The Memorial Hospital, Pawtucket, RI
Gregory L. Burke	Bowman Gray School of Medicine, Winston-Salem, NC
Philip Greenland	Northwestern University Medical School, Chicago, IL
Richard H. Grimm	University of Minnesota Medical School, Minneapolis, MN
W. Dallas Hall	Emory University School of Medicine, Atlanta, GA
Maureen Henderson	Fred Hutchinson Cancer Research Center, Seattle, WA
Lewis H. Kuller	University of Pittsburgh School of Public Health, Pittsburgh, PA
Robert D. Langer	Department of Community and Family Medicine, University of California, San Diego, CA
Norman L. Lasser	University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ
JoAnn Manson	Brigham & Women's Hospital, Boston, MA
Thomas E. Moon	Disease Prevention Center, University of Arizona, Tucson, AZ
Albert Oberman	University of Alabama, Birmingham, AL
Maurizio Trevisan	Department of Social and Preventive Medicine, State University of New York, Buffalo, NY
John A. Robbins	School of Medicine, University of California, Davis, CA
Robert Wallace	University of Iowa College of Medicine, Iowa City, IA

A Series of Overlapping Studies

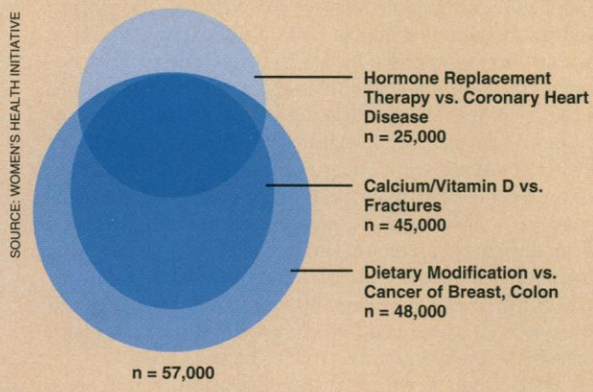
The Women's Health Initiative is really several studies in one: a clinical trial, an observational study, and an educational "community trial." They all have the same broad objective: to study significant causes of death and injury among older women.

The central and most expensive part is the clinical trial, due to begin in September 1993. It will enroll 57,000 women aged 50 to 79 and follow them for 9 years, for a cost, NIH says, of "over $600 million." It is not only large, but quite complex in design. There are three subdivisions—an experiment testing the effects of a low-fat diet on incidence of breast and colon cancer, a second on hormone therapy's role in reducing risk of coronary heart disease, and a third that will test whether daily calcium/vitamin D supplements can help prevent bone fractures and reduce colon cancer risks.

NIH's program officer for the trial, Jacques Rossouw, says volunteers will be invited first to join either the low-fat diet regimen or the hormone therapy part of the clinical trial. Those who join one will be encouraged to join the other. One year after a subject enters the trial, she will be asked to join yet a third segment, the one designed to test the value of calcium and vitamin D supplements. The result: The studies will overlap, with some subjects enrolled in all three segments, others in two, and still others in just one (see diagram). This means that researchers should be able to detect any effects not only of individual therapies but of various combinations of therapies as well.

When NIH invited scientists to compete for contracts last year, it got 61 applications to run the first batch of 14-year contracts to run centers. Of these, NIH chose 16 to help launch the project and test its methodology as "vanguard centers" (see table). NIH will invite applicants to compete again this fall for another 29 center contracts. The entire project will be coordinated by a single data-gathering office. Only one candidate applied for (and won) that contract: the Fred Hutchinson Cancer Research Center in Seattle.

The second element of the overall Women's Health Initiative is the observational study, an epidemiological study that will simply follow for 9 years women who are either unwilling or unable to participate in the clinical trial. It is designed to collect data from an estimated 100,000 women, in an attempt to get a better idea of how factors such as lipid levels, blood pressure, smoking habits, and hormone levels affect risks for cardiovascular disease, cancer, and bone fracture. It will also get under way this fall.



Statistical power. Overlap between the three clinical studies should pinpoint effects of combinations of therapies and generate a lot of data per participant.

Third is the community trial, which is not well defined at this writing. The goal is to target certain communities and educate them intensely on measures individuals can take to improve their health —such as reducing fat in the diet, eating more fiber and vegetables, and stopping smoking. Over time, epidemiologists would compare the relative health of subject and control communities to see whether the education effort was paying off. No protocol has been drawn up as yet.

–E.M.

Listen, for example, to Diana Petitti, an epidemiologist at the University of California, San Francisco, and one of the 42 woman scientists who signed the letter to Healy in 1991 criticizing the study. Petitti says the planning process has been downright "secretive." Bush, of Johns Hopkins, agrees, claiming it was difficult for a while even to get information on who the principal investigators would be. Reflecting the view that the project was designed largely by NIH staff working in isolation, Rosenberg quips that the "study was put together in a dark room."

Healy says such criticism should be taken with a grain of salt, pointing out that the clinical trial was reviewed and given high marks by two panels, one of which included scientists from outside NIH. And during the advisory council meeting, Harlan and Rossouw pledged to send out more information—by the ton—including the 5-volume, 2500-page operating manuals being prepared for the clinics.

Some advisory panel members also questioned whether it's not just the design but also the operation of the project that's being limited to a tightly knit club. Or, as panel chair Virginia Weldon of Monsanto put it: "Why is an initiative on women's health being led by men?" The basis for the question is that 13 of the 16 principal investigators and the director of the coordinating center, the Fred Hutchinson Cancer Research Center in Seattle, are male.

"Sadly," Healy comments, the male leadership "reflects the history" of biomedical research. Men have dominated the field for years, she said, and it should be no surprise that some of the best resumes in the business belong to men. Although she hopes to promote women's careers, Healy says, "women can advance without having a handicap put on men....We do not introduce gender into our priority scores. I do not think we should, and I hope we never do."

Focus on diet

Much of the substantive criticism of the clinical study has been focused on the effort to test whether a low-fat diet will reduce the risks of breast and colon cancer. Although this is only one of the three overlapping clinical trials, it is in many respects central to the whole effort. It will involve the largest group of subjects (48,000 women), many of whom will also be enrolled in one or both of the other two trials—the hormone therapy and the tests of dietary supplements. Critics believe the clinics will have a hard time recruiting a socially diverse group of women and persuading them to follow an austere diet (20% fat) for 9 years. And even if recruitment is successful, they contend that the study is unlikely to produce a definitive result. The bottom line: If the dietary study is not viable, why not simply test the other two therapies separately in smaller, more focused studies?

The rationale for the low-fat diet study is to try to nail down an association that some previous studies have hinted at. For example, a meta-analysis of 12 case-control studies by Geoffrey Howe of the University of Toronto indicated that women on a low-fat diet did in fact have a slightly lower breast cancer risk than controls. But other credible studies have provided no evidence to justify an expensive trial such as this.

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

persuading the community that its projected cost estimates are credible. Willett, for example, says he thinks the clinical trial will cost about $1 billion before it's done. Another epidemiologist running a major women's study funded by NIH says it will cost "easily a billion," probably more.

Greenland notes that NIH designed the trial with many overlapping studies in order to get a big payoff in data for the amount of money invested. But he conceded that if women fail to sign up for more than one study, this efficiency will slip away. And if the cost were to increase dramatically, "people would seriously question" whether NIH should spend $1 billion on the project.

NIH has been pressuring the clinics to pare their budgets down to the bare essentials, and Rossouw confidently predicts that this complex undertaking can be run at one-sixth to one-third the usual per-participant cost of an NIH trial. Yet Congress was surprised when NIH's estimate of the cost increased from $500 million to $619 million last year. The House appropriations subcommittee on health was so rattled, says a staffer, that it decided to order a study before committing more money. The House asked NIH to contract for an independent analysis of the project through the Institute of Medicine (IOM). The bill called for delivery of a report in February 1993, but it's taken longer than expected. IOM only got a contract 2 weeks ago, and the report won't be done until September—perhaps after the clinical trial has begun.

The IOM review panel will focus mainly on cost, but may look into the study's design, and it may also invite public comment this summer. Even some of the skeptics say, however, that at this late stage they just hope to steer the trial away from major pitfalls so that it can achieve some of its ambitious goals. Says one NIH-funded scientist who asked to remain anonymous, "We see a very powerful train moving very fast; getting in the way of it could be injurious to one's own health."

–Eliot Marshall

National Academy Elects New Members

Seven women and 53 men were elected to membership in the National Academy of Sciences last week, and 15 were elected as Foreign Associates. The new members are:

Aharonov, Yakir, Tel Aviv University, Israel, and University of South Carolina; **Ahlquist, Paul G.**, University of Wisconsin, Madison; **Atal, Bishnu S.**, AT&T Bell Laboratories, Murray Hill, New Jersey; **Baker, Bruce S.**, Stanford University; **Baldwin, Ransom Lee, Jr.**, University of California, Davis; **Baylor, Denis**, Stanford University; **Beasley, Malcolm R.**, Stanford University. **Biemann, Klaus,** Massachusetts Institute of Technology; **Canizares, Claude R.**, Massachusetts Institute of Technology; **Casey, Charles P.**, University of Wisconsin; **Caskey, C. Thomas**, Howard Hughes Medical Institute, Baylor College of Medicine; **Chipman, John S.**, University of Minnesota, and University of Konstanz, Germany.

Chu, Steven, Stanford University; **Cocke, John**, Thomas J. Watson Research Center, Austin, Texas; **Collins, Francis S.**, Howard Hughes Medical Institute, University of Michigan Medical School; **Cook, R. James**, Agricultural Research Service, Washington State University, Pullman; **Crandall, Stephen**, Massachusetts Institute of Technology; **Dalrymple, Brent**, U.S. Geological Survey, Menlo Park, California; **Davis, Mark M.**, Howard Hughes Medical Institute, Stanford University; **DePaolo, Donald J.**, University of California, Berkeley; **Friedman, Avner**, University of Minnesota; **Garbers, David L.**, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas; **Gollub, Jerry P.**, Haverford College and University of Pennsylvania; **Golub, Gene H.**, Stanford University; **Gorski, Jack**, University of Wisconsin.

Guthrie, Christine, University of California, San Francisco; **Harlow, Edward E., Jr.**, Harvard Medical School and Massachusetts General Hospital; **Hendrickson, Wayne A.**, Howard Hughes Medical Institute, Columbia University; **Howley, Peter M.**, National Cancer Institute; **Huchra, John P.**, Smithsonian Institution and Harvard University; **Inoué, Shinya**, University of Pennsylvania and Woods Hole Marine Biological Laboratory; **Klausner, Richard D.**, Uniformed Services University of the Health Sciences and National Institute of Child Health and Human Development.

Kleckner, Nancy E., Harvard University; **Kornberg, Roger D.**, School of Medicine, Stanford University; **Kustu, Sydney,** University of California, Berkeley; **Labov, William**, University of Pennsylvania; **Langlands, Robert**, Institute for Advanced Study; **Long, Sharon R.**, Stanford University; **Maccoby, Eleanor E.**, Stanford University; **Mao, Ho-kwang (David)**, Carnegie Institution of Washington (D.C.); **Marks, Tobin J.**, Nothwestern University; **McKelvey, Richard D.**, California Institute of Technology; **Merton, Robert C.**, Harvard University; **Modrich, Paul L.**, Duke University; **Molina, Mario J.**, Massachusetts Institute of Technology; **Murray, Joseph E.**, Harvard Medical School; **Navrotsky, Alexandra**, Princeton University; **Netting, Robert M.**, University of Arizona; **Ratner, Marina**, University of California, Berkeley; **Rice, T. Maurice**, Eth-Honggerberg, Zurich, Switzerland; **Rothman, James E.**, Sloan-Kettering Institute, New York City.

Schultz, Peter G., University of California, Berkeley; **Smelser, Neil J.**, University of California, Berkeley; **Squire, Larry R.**, University of California, San Diego, and Veterans Affairs Medical Center, San Diego; **Stone, Charles J.**, University of California, Berkeley; **Tigner, Maury**, Cornell University; **Uhlenbeck, Olke C.**, University of Colorado; **Vande Woude, George F.**, National Cancer Institute, Frederick Cancer Research and Development Center; **Williams, George C.**, State University of New York at Stony Brook; **Yau, S.T.**, Harvard University.

New foreign associates are:

Bartlett, Maurice S., University of Oxford (England); **Blackburn, Elizabeth H.**, University of California, San Francisco (Australia); **Busse, Friedrich H.**, University of Bayreuth (Germany); **Clarke, Adrienne E.**, University of Melbourne (Australia); **Dobrushin, Roland L.**, Institute for Problems of Information Transmission, Russian Academy of Sciences, Moscow (Russia); **Drèze, Jacques H.**, Université Catholique de Louvain (Belgium); **Fersht, Alan R.**, University of Cambridge (England); **Friesen, Henry G.**, Medical Research Council of Canada; **Sakmann, Bert**, University of Göttingen and Max Planck Institute for Medical Research, Göttingen (Germany); **Sarukhán, José**, Universidad Nacional Autonoma de Mexico, Mexico City (Mexico).

Sato, Mikio, Research Institute for Mathematical Sciences, Kyoto University (Japan); **Sobolev, Nikolai V.**, Institute of Geology and Geophysics, Siberian branch, Russian Academy of Sciences, Novosibirsk (Russia); **Taylor, Richard E.**, Stanford University (Canada); **Valyasevi, Aree**, Institute of Nutrition, Mahidol University, Bangkok (Thailand); **Van Rood, Johannes J.**, Leiden Institute for Immunology (Netherlands).