

Recruitment *and*
Retention of
Women in
Clinical Studies

A REPORT OF THE
WORKSHOP
SPONSORED BY THE
OFFICE OF RESEARCH ON
WOMEN'S HEALTH



OFFICE OF THE DIRECTOR
NATIONAL INSTITUTES OF HEALTH

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Retention of
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Clinical Studies

OFFICE OF RESEARCH ON WOMEN'S HEALTH
OFFICE OF THE DIRECTOR
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CONTENTS

FOREWORD

i

Ruth L. Kirschstein, M.D.
Deputy Director, National Institutes of Health

PREFACE

iii

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health
National Institutes of Health

INTRODUCTION

v

Shiriki R. Kumanyika, Ph.D., M.P.H.
Lewis H. Kuller, M.D., Dr.P.H.

PREPARED REMARKS OF CONGRESSWOMAN LOUISE M. SLAUGHTER (D-NY) TO THE OFFICE OF RESEARCH ON WOMEN'S HEALTH SCIENTIFIC MEETING

vii

Recruitment and Retention of Women in Clinical Studies
Exclusion of Women
Women's Health Equity Act
Women's Health—A Movement
Women in Health Care Reform
Conclusion

CHAPTER 1: OVERVIEW OF RECRUITMENT AND RETENTION ISSUES

1

Shiriki R. Kumanyika, Ph.D., M.P.H.
Lewis H. Kuller, M.D., Dr.P.H.

CHAPTER 2: DESIGN AND IMPLEMENTATION ISSUES IN CLINICAL STUDIES

3

Carol K. Redmond, Sc.D.
Julie E. Buring, Sc.D.
Introduction
Key Design and Implementation Issues
Summary and Recommendations

CHAPTER 3: INVESTIGATOR AND INSTITUTIONAL ISSUES IN THE RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES

7

Maureen M. Henderson, M.D., D.P.H.
Marion M. Lee, Ph.D., M.P.H.
Introduction
An Overview of Clinical Studies
Key Investigator and Institutional Issues
Benefits and Risks to Investigators in Conducting Clinical Studies
Summary and Recommendations

CHAPTER 4: PARTICIPANT AND COMMUNITY ISSUES IN THE RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES

17

Barry D. Kaufman, D.M.D.
Helen Rodriguez-Trias, M.D.
Introduction
Key Issues
Summary and Recommendations

CHAPTER 5: CURRENT EXPERIENCES IN WOMEN'S HEALTH RESEARCH**25***Lewis H. Kuller, M.D., Dr.PH.*

Introduction

Recruitment Strategies

Retention Strategies

Other Examples of Successful Clinical Studies Involving Women

Summary

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS**29***Summary List of Recommendations*

APPENDICES**33***Appendix I***35**

Task Force Roster

*Appendix II***39**

Public Hearing Summary

*Appendix III***61**

Agenda

*Appendix IV***67**

Speakers

*Appendix V***73**

Observers

*Appendix VI***93**

Legal and Ethical Issues

*Appendix VII***99**

Lesbians in Health Research

FOREWORD

Recruitment and Retention of Women in Clinical Studies

Interest in women's health issues has existed for a long time but has only gained prominence and momentum in the last decade. In 1983, I chaired the newly established Public Health Service (PHS) Task Force on Women's Health Issues. This task force examined women's health issues across the lifespan, particularly in the context of sociological changes experienced by our Nation during the late 20th century.

One of the most important recommendations that emerged from the task force's report *Women's Health Report of the Public Health Service Task Force on Women's Health Issues* was that biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women of all ages. As a first step toward implementing this recommendation, the National Institutes of Health (NIH) developed and published a policy statement urging grant and contract applicants to include women in clinical research.

Although the policy was implemented, concerns were expressed by many, including members of Congress, about whether efforts to enhance the participation of women and minorities as research subjects were being taken seriously by the scientific community in general and by NIH in particular.

As a result of these concerns, in 1989, the General Accounting Office (GAO) was asked by Congress to review the NIH inclusion policy,¹ specifically compliance by grant applicants and policy monitoring and implementation by the NIH. A major finding of the GAO's June 1990 report was that more uniform implementation and monitoring of the inclusion policy were needed.

Following publication of the GAO report, the NIH issued a revised, strengthened policy on the inclusion of women and minorities in clinical research. The policy stated that no funding would be awarded to applicants who do not show adequate representation of women in planned clinical research unless compelling justification was provided. NIH began to apply this new policy to research contracts and to clinical research conducted in intramural and extramural programs.

The release of the PHS Task Force on Women's Health Issues report and the establishment and strengthening of the NIH inclusion policy provided a unique opportunity for the U.S. Department of Health and Human Services (DHHS) to reassess its policies and focus attention on the health of American women. This opportunity was realized

when the Office of Research on Women's Health (ORWH) was created on September 10, 1990. I was honored to serve as its first acting director. One of the office's primary objectives was to reinforce the implementation of the NIH policy, and, perhaps more importantly, to change the culture surrounding the development and review of clinical trials.

On June 10, 1993, the focus on issues related to women's health was firmly established in law with the passage of the National Institutes of Health Revitalization Act of 1993.² Its provisions include the statutory establishment of the ORWH; an Advisory Committee on Research on Women's Health, which is to advise the ORWH on appropriate research activities to be undertaken by the NIH; and a statutory mandate for the inclusion of women and minorities as subjects in clinical research funded by the NIH.

The passage of this legislation underscored continuing congressional concern about research on women's health issues and congressional support of the ORWH's research and policy activities and the NIH's demonstrated leadership in this area.

Although many in the scientific community have strongly embraced the need for expanded study populations, barriers to the full inclusion of women and minorities in clinical research remain. *Recruitment and Retention of Women in Clinical Studies* takes a focused and thorough look at these issues. It identifies barriers to recruitment and retention and offers concrete and viable recommendations. The discussions and recommendations are based on the experience of numerous nationally recognized experts from diverse fields. This report is invaluable to the scientific community, industry, academia, Congress, advocacy groups, and the public. It demonstrates NIH's firm commitment to improving the health of American women and, thus, the health of the Nation.

Ruth L. Kirschstein, M.D.
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National Institutes of Health
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of Research on Women's Health

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PREFACE

Attention to the inclusion of women in clinical research has become a far-reaching priority for members of Congress, the scientific community, and women's advocacy groups. It is also central to the mandate for the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) and its commitment to improving the health of women and minorities.

The ORWH's mandate is to give the NIH a central focus on women's health issues and to establish a science base that will permit reliable diagnoses, effective treatment, and preventive strategies for women.

The major objectives of the ORWH are to:

- Develop an integrated strategy for increased research into diseases, disorders, and conditions that are unique to, more prevalent among, or more serious in women or for which there are different risk factors or interventions for women than for men.
- Ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially in clinical trials that are supported by the NIH.
- Direct initiatives to increase the number of women who participate in biomedical research careers.

The second objective, which is among the highest of the ORWH's priorities, addresses the participation of women in study populations, especially clinical trials. Women cannot expect to gain equitably from new advances in therapy and interventions if they are not included in the clinical trials that assess safety and efficacy.

The current NIH policy on the inclusion of women and minorities in study populations clearly states that women shall be included in clinical studies in numbers proportional to the prevalence among women of the condition under study. To monitor compliance with this policy, the ORWH instituted a tracking system and is beginning to analyze the results from the system's first year of implementation.

In addition, the ORWH has examined why women are all too often excluded from research. Two of the most commonly stated reasons for this exclusion are the legal and ethical issues surrounding potential exposure and risk to a fetus and the difficulty of recruiting women into studies. Regardless of whether this exclusion is an act of discrimination or of protection, it must be rectified immediately. In addition, most developing therapeutic modalities, biotechnological advances, preventive interventions, or predictors of health or disease outcome will, by necessity, not only be applicable to men. They must also be

applicable to a wide spectrum of women, including those who are pregnant, of childbearing potential, elderly, lesbian, of diverse racial or ethnic origin, of varied socioeconomic status, from rural areas, from inner cities, or homeless. Therefore, it is imperative that we know and understand the potential effects of diagnostic efforts, treatment, and prevention in these populations and not just infer their applicability to women based on studies conducted in men.

The NIH is now in the process of establishing guidelines to implement recent congressional mandates for the inclusion of women and minorities in NIH-funded research. The NIH, in conjunction with the Institute of Medicine (IOM), is addressing the legal and ethical implications that investigators and administrators face as they attempt to include more women in clinical studies while keeping women's health and the health of any potential fetus at the forefront of research considerations.

There is also the need to recruit and retain women in clinical studies if we are to fill in the gaps in our knowledge of women's health. To assist in this endeavor, the ORWH formed a Task Force on the Recruitment and Retention of Women in Clinical Studies, which held two meetings during 1993: a public hearing in March and a scientific meeting in July. We were honored to have Congresswoman Louise Slaughter as our keynote speaker for the scientific meeting; her perceptive and thought-provoking remarks are included in this report.

In presenting *Recruitment and Retention of Women in Clinical Studies*, which is a summary and synthesis of the two meetings, I wish especially to thank Dr. Shiriki R. Kumanyika and Dr. Lewis H. Kuller, who served as co-chairs of the task force; the other members of the task force; and those who provided testimony at the public hearing. The time, experience, and expertise given by these individuals and by the other participants in the meetings are clearly reflected in this report. Their contributions will be of invaluable assistance as the NIH continues its efforts toward meeting the goal of full inclusion of women and minorities in clinical research.

Vivian W. Pinn, M.D.
Associate Director for Research
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INTRODUCTION

In order to explore the issue of the participation of women and minorities in clinical research and to develop strategies for promoting the full inclusion of these groups, the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) formed the Task Force on the Recruitment and Retention of Women in Clinical Studies. The task force held a public hearing in Bethesda, Maryland, on March 29-30, 1993. Thirty-nine individuals and organizations presented testimony at the hearing; an additional 19 individuals and organizations submitted written testimony. These testimonies addressed the social, economic, and health experiences of many women in this country; the need for including women in clinical studies; and the barriers to women's participation.

The information gathered by the task force at the public hearing was used to plan a scientific meeting that was held on July 12-13, 1993, in Bethesda, Maryland. The objectives of this meeting were to generate recommendations for action, develop strategies for fostering the participation of women and minorities in clinical research, and highlight successful instances for recruitment and retention of women and minorities into research studies.

Participants in the scientific meeting discussed these issues in a series of panel sessions, corresponding to the topics covered in chapters 1, 2, 3, and 4 of this report. Each panel session was led by two comoderators. Statements and presentations made by individuals and representatives of national organizations during the scientific meeting clearly supported the view that a much broader inclusion of women in clinical research studies is necessary. Perhaps even more important, these statements and presentations showed that this goal is, indeed, attainable.

Recruitment and Retention of Women in Clinical Studies presents a summary and synthesis of results from the public hearing and the scientific meeting. It is organized into chapters, each of which considers a key aspect of the issue of recruitment and retention of women in clinical studies. Chapter 1 presents an overview of historical issues in women's health and women's participation in clinical research. Chapter 2 looks at study design and implementation issues and how they affect the participation of women and minorities in clinical studies. Chapter 3 explores some of the major investigator and institutional issues that hamper the inclusion of women and minorities in clinical research. Chapter 4 examines the inclusion issue from the viewpoint of the participants

and the community and looks at such areas as beliefs and attitudes, appropriate communications channels, and logistical barriers to participation. Chapter 5 highlights some success stories: studies in which women and minorities have been effectively recruited and retained and which have resulted in the formation of strong partnerships between the sponsoring research institution and the community. Finally, chapter 6 presents some overall conclusions and a summary list of the recommendations presented in chapters 2, 3, and 4.

Shiriki R. Kumanyika, Ph.D., M.P.H.
Lewis H. Kuller, M.D., Dr.P.H.

REMARKS

Representative Louise M. Slaughter (D-NY)

PRESENTED AT
THE OFFICE OF RESEARCH
ON WOMEN'S HEALTH
SCIENTIFIC MEETING ON
RECRUITMENT AND RETENTION
OF WOMEN IN CLINICAL STUDIES

It is an honor to be with you this morning. The last time I addressed a scientific meeting of the National Institutes of Health was April 1992. We were launching a new, comprehensive initiative by the institutes to consider the lingering health effects of exposure to the pregnancy drug DES. As the author of legislation signed into law to authorize this expanded research and public health education program, I was honored to meet the men and women scientists like yourself, who had dedicated their careers and their very lives to finding answers to the difficult questions of diethylstilbestrol (DES) mothers, sons, and daughters: What has DES done to my body? Will I get cancer? If I do, can I survive?

The questions that you pursue—in the laboratory, in the treatment room, and in conferences like these—are fundamental quality-of-life issues and critical life-or-death questions. It is the noblest of pursuits because biomedical research holds the promise to change lives and save lives. It is simply unfair then, and perhaps even unethical, that until now such promise did not equally apply to female lives.

Exclusion of Women

In 1986, the NIH adopted a policy requiring the inclusion of women in clinical trials, but a 1990 study by the General Accounting Office (GAO) found that the policy was not enforced, leaving women still excluded from the bulk of government-sponsored medical research. You probably know the list even better than I: the diabetes study, the aspirin-a-day study on heart disease, diet pill studies, and studies on the role of iron in cardiovascular disease—all performed primarily on white males. No matter that women are the primary consumers of diet pills and iron supplements or that women and minorities are three times more likely to have diabetes. No matter that heart disease is the number one killer of women. And, no matter that women pay at least one-half of the Nation's tax dollars, the same tax dollars that pay for NIH research.

It has been almost three decades since the Civil Rights Act of 1964 began tearing at the notion that women couldn't hold certain jobs because, surely, we were handicapped by our hormones and menstrual periods. But medical science didn't follow suit. Menstrual cycles and irregular hormone levels were blamed for data too difficult to analyze, becoming a convenient excuse to ignore female subjects in many cases.

But, when it comes to biology, we know that men and women are not created equal. We have different chemistries, different average body weights, different organs. It only stands to reason, then, that we would require different treatments, different dosages, and different means of prevention. But not enough research has been done to figure out just what those differences are. This is changing, obviously, or we wouldn't be here today. A new law signed by President Clinton, the National Institutes of Health Revitalization Act of 1993, requires that women be included in clinical studies for purposes of gender analysis.

Women's Health Equity Act

Perhaps the 1990 GAO report started it all. It was the culmination of a year-long study requested by the Congressional Caucus for Women's Issues in order to determine the extent to which women have been left out of federally funded research. The caucus is made up of all the women in the House of Representatives; at that time, we numbered only 29—just over 6 percent of the House. We may be small in numbers, but we make a lot of noise and wear bright colors to stand out among the navy and gray pinstripes. Well, let me tell you, we made an awful lot of noise about women's health that year in the 102nd Congress.

We introduced an omnibus Women's Health Equity Act, an unprecedented package of 22 separate bills designed to improve the status of women's health in the areas of research, services, and prevention. Among the provisions of this mammoth legislation were: the establishment and permanent authorization of the Office of Research on Women's Health (which has convened this important meeting); the statutory requirement that women and minorities must be included in NIH clinical studies, where appropriate; the establishment of research centers on osteoporosis, contraception, and infertility; and necessary funding increases for research into the diseases that claim unacceptable numbers of female lives, like breast, ovarian, and cervical cancers.

We also authorized an expansion of existing studies on conditions like lung cancer, heart disease, and acquired immune deficiency syndrome (AIDS) so that researchers could look specifically at gender differences in risks, symptoms, and treatment protocols.

Even before the reinforcements arrived in the 103rd Congress—22 new women were elected to Congress last November—we made some remarkable progress in passing

certain elements of the Women's Health Equity Act. We enacted legislation establishing a \$25 million program to prevent infertility through screening and treatment of chlamydia and other sexually transmitted diseases. We also passed legislation setting Federal standards for mammography facilities.

Many of the remaining provisions of the Women's Health Equity Act were included in the NIH bill that was vetoed by President Bush because his administration opposed lifting the ban on fetal tissue research and objected to the women's health section of the bill as "unnecessary." Thankfully, President Clinton made the NIH bill, and especially its critical improvements of women's health research, one of his first legislative priorities. It was signed on June 10, 1993, in a White House ceremony befitting such historic legislation.

Much remains to be done in the area of women's health, and this year we will again introduce an omnibus Women's Health Equity Act. It will address, among other issues: women and AIDS, women and alcoholism, lupus, RU486 research, pharmaceutical interactions and testing, teen pregnancy, and menopause. And, as a caucus, the women in Congress have already met with Mrs. Clinton and testified before the Ways and Means Committee in order to make sure that women's special medical needs are included in national health care reform.

Women's Health—A Movement

How did we get to where we are today? Nineteen ninety-two was popularly billed as the "Year of the Woman," but what confluence of political, social, and economic factors conspired to make it so? How did women's health become almost a movement, a revolution?

When Anita Hill showed the Nation how absurdly out-of-touch a nearly all-white-male Congress is with the American woman, American women started looking into all the other areas of public policy where their interests were being neglected, including employment, education, criminal justice, and health care. An analysis of Government funding spent for cancer research revealed that relatively little was being spent on "female" cancers like ovarian, breast, and cervical cancers. It was appalling to learn that we have a blood test for the early detection of prostate cancer, and yet we have no way to detect ovarian cancer until it has become a death sentence.

As a member of the House Budget Committee, I worked with the Breast Cancer Coalition in the 102nd Congress

to secure an ambitious increase in breast cancer research funding of \$300 million. In the budget resolution, I included that funding goal for breast cancer on top of \$200 million in additional increases for women's health research. It was the first time women's health was specifically designated in the budget resolution, and as one of only two women on the Budget Committee that year, I believe it was probably the first time the words breast and cervix were spoken in the budget hearing room.

In the Budget Committee of the 102nd Congress, I began a debate that continues today, especially as resources become more and more scarce. It simply makes no sense to me that we can spend \$3.8 billion on "Star Wars" against a nonexistent enemy and yet struggle for a \$300 million appropriation to combat breast cancer—a very real enemy that kills at least 46,000 American women in a single year.

But the debate is not only one of ordering priorities like defense over health care or education over criminal justice. It is also a commonsense debate about how a small investment in biomedical research and prevention can yield substantial savings in medical expenses. Until recently, however, we neglected that investment by letting the NIH budget stagnate; by refusing Medicare and Medicaid coverage for services like screening mammograms, Pap smears, and vaccines; and by allowing private health insurance companies to deny such coverage as well.

We've paid for this neglect. We've paid heavily. We spend \$289 billion on hospital services each year. We spend another \$142 billion on physician services. And we spend \$61 billion each year on prescription drugs and other medical nondurables.

But all this money, in sums too great even to comprehend, has not bought us, as a population, good health. Our health care system, the most expensive in the world, has failed us.

Women in Health Care Reform

By failing to guarantee access to preventive health services, our current health care system has allowed the death toll for breast cancer to rise to epidemic proportions. By failing to provide lifesaving vaccines to adults and children, our current system has allowed the incidence of rubella and measles to increase fivefold since 1987. Over the past 3 years, we've sent 54,000 Americans to hospitals with measles, watching more than 100 of those adults and children die from this entirely preventable disease.

And, until we ensure coverage for a full range of primary and preventive reproductive health care services—including family planning and contraception—we can do nothing to reduce the appallingly high rates of teen pregnancy, infant mortality, and babies born drug addicted or infected with HIV, all of which ultimately impose costly burdens not only on our health care system but also on our schools, our housing programs, our criminal justice system, and the national economy in general.

National health care reform is one of the most difficult and complicated issues that the 103rd Congress will address, but, essentially, the current debate comes down to compassion versus cost savings. One side argues that health care is a right and that quality-of-life considerations must be the guiding force of reform. The other side insists that controlling runaway health costs must be our primary objective. I submit to you, and I think you will agree, that both objectives can be achieved through a commitment to preventive health and the biomedical research that leads to more effective means of prevention.

If we can successfully shift the primary mission of health care away from curing sickness to understanding sickness and maintaining wellness, we will simultaneously realize both a dramatic increase in quality of life and meaningful savings in health care expenditures.

Our experience with breast cancer provides a compelling example. A mammogram is a simple X ray that costs under \$100 per screening. Without the \$100 investment in a screening mammogram, breast tumors are not likely to be identified until they have grown to the size of a marble or even a Ping-Pong ball. At this point, the tumor is not only more deadly, it is more expensive. Treatment costs for advanced-stage breast cancer soar to an average of \$84,000 per patient—all because the opportunity for early detection was missed.

As chair of the Women's Caucus Task Force on Women's Health, I'm working to make sure that any new plan for health care in the United States adopts biomedical research and prevention as its primary emphases. We have both the know-how for cutting-edge research and the technology for prevention and early detection. It's unforgivable that we haven't yet been completely successful in transferring what we've learned in the laboratories to what we practice in the doctor's offices. Such is the drum I beat for this Congress, as we undertake national health care reform.

Conclusion

We must have a system that includes fundamental primary and preventive services, especially those unique to women because, unless the women of this country are healthy, we offer no hope of healthy children. And, let's face it, when we consider that women make up the fastest growing segment of the labor force and that women are starting up their own businesses at a rate at least four times greater than that of men, we realize that we cannot afford to rest the Nation's economic future on the stooped shoulders of women crippled by osteoporosis or weakened by breast cancer. I say to the women in the audience: Ladies, we are more than 100 million strong—more than 50 percent of the Nation's population. If we are not healthy enough to do the Nation's grocery shopping, raise the Nation's children, manage the Nation's business, educate the Nation's youth, clean up the Nation's forests and oceans, and make the Nation's laws, I don't know what kind of future the Nation can expect. The women's health movement is not a passing fad, it is truly a revolution for the 1990's and the 21st century.

OVERVIEW OF RECRUITMENT AND RETENTION ISSUES

Shiriki Kumanyika, Ph.D., M.P.H.

Lewis H. Kuller, M.D., Dr.P.H.

Until well into the 20th century, there was very little examination of the health of American women beyond reproductive issues. A review of the medical and scientific literature of the late 1800's and early 1900's shows that, although women may have suffered from other ailments, the medical and scientific attention that was paid to women centered around questions of hormones, reproduction, and childbearing.¹ A number of reasons can be cited to explain this situation. The medical community's ability to define completely the range and nature of women's health problems was limited by the absence of measurement and documentation systems or by the need to rely on systems still in formative stages. The state-of-the-science did not allow for significant collection and recording of data on Americans' overall health and was particularly lacking in the areas of women's, and especially minority women's, health care issues. Other reasons for the insufficient attention to women's health included restrictive social conventions that gave rise to discrimination, biases, and stereotypes and resulted in a diminished status for women and their roles in family and society.

It was not until this century that medical research into women's health care issues began to expand beyond gynecological and reproductive health. With increases in funding, especially Government funding, and rapid technological development, the ability to conduct scientific research in many areas affecting the health of women and men increased markedly.¹

A major development in the conduct of scientific research on humans came about with the use of randomized clinical trials and other types of human clinical studies beginning in the 1940's and 1950's. Information gained from these studies led to an enhanced understanding of the causal factors in and optimum treatments for a broad range of diseases, particularly chronic diseases.

As investigators began to rely more heavily on clinical studies, two issues in study designs became crucially important. The first was cost, particularly in the cases of studies that required large sample populations and many years to complete. The second issue was complexity. Investigators felt that the best studies were simple in design and involved the fewest number of variables. Involving women in clinical studies was viewed as not only increasing the complexity of the study design because investigators would have to take into account hormonal fluctuations and other gender-based differences but also as increasing the costs due to increased sample sizes, particularly in studies where the disease-event rate might be lower in women than in men (e.g., coronary heart disease).

In addition to these factors, other concerns contributed to the underrepresentation and even exclusion of women from clinical studies. The tragic discoveries of the immediate or delayed teratogenic effects of certain drugs such as diethylstilbestrol (DES) and thalidomide led the Food and Drug Administration (FDA) to develop more stringent policies on the inclusion of women of childbearing potential in Phase I and early Phase II clinical studies.¹

During the last decade, a number of forces have come together to begin to change the situation with respect to research on women's health. The demographic, environmental, and societal changes that are occurring in the United States are fostering collaboration between health researchers from all disciplines and the public to promote health and well-being. Increasingly large segments of the American public are informed about, aware of, and committed to participating in biomedical research efforts. The American public is also exercising its prerogative to request, and at times demand, greater accountability for expenditures of their tax dollars in biomedical research. Women's health and AIDS are but two examples of issues in which consumer activism is playing an increasing and constructive part in developing the research and treatment agenda at the Federal, state, and local levels.

A visible result of these changes was the June 10, 1993, signing of the National Institutes of Health Revitalization Act of 1993 by President Clinton. This act statutorily requires that women and minorities be included in research that is supported by Federal funds.

Since its inception in September 1990, the ORWH has been the focal point for women's health research policy development funded by the NIH and for the creation of mechanisms to promote and monitor the inclusion of women and minorities in clinical studies. The ORWH shares the leadership for this latter responsibility with the Office of Research on Minority Health, the Office of Extramural Research, and the Office of Intramural Research, all of which are under the auspices of the Office of Director of the NIH.

A major focus of the ORWH's work, in collaboration with the administrators and staff of NIH's 24 constituent institutes, centers, divisions, and offices, is to support scientific endeavors that will provide data necessary to improve the health and quality of life of American women. The forging of such partnerships has created a heightened awareness of women's health issues and a fuller recognition of women's health as a priority in the research activities of the NIH and the broader scientific community.

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DESIGN AND IMPLEMENTATION ISSUES IN CLINICAL STUDIES

Carol K. Redmond, Sc.D.

Julie E. Buring, Sc.D.

Introduction

The primary goal of any clinical study should be to provide either a definite positive result on which individual clinical decisionmaking and public health recommendations can be reliably based or an informative null result that will safely permit the rechanneling of research and resources into more promising areas.

Including women and minorities in clinical studies may introduce special scientific and logistical issues, while concurrently creating opportunities for identifying and addressing new areas of research. Investigators can address these issues through the creation and development of innovative designs, and they may identify cost-effective options by considering alternative strategies for the study design. The unique strength of a well-designed and conducted study involving women and minorities is its ability to provide information of direct benefit to these populations, enabling health professionals from many disciplines to make better informed judgments about treatment and care. In addition, results from such studies can enable policymakers at all levels to improve the overall health of Americans.

Conducting a clinical study that provides an analysis of whether the interventions or variables studied are efficacious and safe for the specific groups of interest requires a strong commitment to maintaining the scientific integrity of the study. Such a commitment is crucial in every aspect of the study's design, conduct, analysis, and interpretation. A clinical study that is not properly designed and implemented can provide misleading or incorrect information that may, in fact, prove more detrimental than having no information at all. Any issues or factors that could threaten the validity of a study must be identified and addressed in the study design.

Scientific investigators have a special responsibility to consider and carefully monitor the balance between validity and the ability to generalize research findings and analyses. The heterogeneity of study populations has historically been thought to ensure that research findings can be generalized to other groups. On the other hand, the validity of study results, that is, the assurance that the exposure or intervention *itself* is responsible for the observed effects, is enhanced by studying homogeneous populations to eliminate differences among the groups that might lead to spurious results. It is crucially important to recognize that the first requirement for generalizing a study result is that it be valid—an invalid result simply cannot be generalized to any group. The need for scientific

validity must be balanced against the need for heterogeneity of subjects so that results can be generalized to the broadest possible population.

Key Design and Implementation Issues

Key design and implementation issues of particular importance in relation to the inclusion of women or minority women in clinical studies are discussed below. Although many of these issues may be applicable for all clinical study populations, studies specifically targeting women or minorities may differ in specification of the research questions, and special study design and implementation approaches are often necessary to ensure adequate recruitment and retention of these groups in study cohorts. At the same time, investigators must ensure that the data obtained on these groups are valid. Therefore, it is crucial to consider how characteristics of study participants relate to the design, conduct, analysis, and interpretation of the study. These considerations are important to consider in addition to the traditional scientific issues.

THE RESEARCH QUESTION

The composition of the study population is directly related to the question being addressed in a scientific study because disease incidence, prevalence, and mortality—as well as associations of risk factors with disease occurrence—may differ by gender and across different racial and ethnic groups. For example, African-American, Hispanic, and Native American women have been shown to have higher rates of diabetes, hypertension, and obesity than Caucasian women, and associations of varying magnitudes of these conditions with mortality are observed across race and ethnicity.^{1,2,3} Different approaches to interventions or treatments are sometimes needed by different groups. Quantitative differences, or differences in the magnitude of the benefits and risks may often exist, but even qualitative differences, in which different groups respond to the intervention or treatment in an opposite manner, are sometimes observed.

DESIGN AND STUDY METHODOLOGY

Many factors regarding methodology must be considered when planning a clinical study that includes women, minorities, or those from diverse socioeconomic strata as participants. For example, the need for keeping a study concise must be weighed against the desire for collecting as much data as possible, which could require a more complicated study. A concise study does not overtax participants with unnecessary tests and allows straight-

forward inference and interpretation. On the other hand, studies of diverse populations may require more complex assessments to achieve a similar level of validity within each subgroup. Furthermore, in a more complex study investigators may collect a large amount of data that can be used to address a number of research questions from one study rather than attempting to study the same population repeatedly. Collecting the required amount of data is also important because certain types of clinical studies, as a result of their high cost, can be conducted only once.

Another consideration when deciding on study methodology is how to balance design features that are necessary to ensure the validity of a trial with issues that could create barriers to participation. Using a double-blind study design and incorporating a placebo into a trial may be necessary for controlling bias and thus assessing subjective outcomes and side effects. Also, random allocation is critical because it is the only strategy that can achieve control of both known and unknown confounding variables. However, these and other design features may create barriers to the participation of low-income women, for example, because they may view study participation as a means to obtain otherwise unavailable health care services. Some women may fear being randomly assigned to a group and not knowing if they are receiving an intervention. These fears may arise legitimately from the sometimes unfortunate history of women and minority populations as participants in research studies. However, because these design features may be essential to preserve the validity of the study, special educational efforts may be required so that incorporating these features does not create barriers to participation and, ultimately, to the study's success.

SAMPLE SIZE

The issue of adequate sample size is another critically important aspect of study design that is affected by the nature of the study population. If the sample size is inadequate to answer the question posed, investigators run the risk of obtaining an informative null result, that is, a finding that is not statistically significant because the study did not have adequate power to detect an effect even if one were, in fact, present. Such results can be scientifically very harmful; they are likely to be misinterpreted as indicating no effect, when, in fact, the effect simply could not be detected.

The exact sample size needed will depend directly on the particular question. For example, a study in which the investigators' goal is to evaluate efficacy or side effects separately for women and men or for different ethnic groups would require a substantially larger sample than a study that simply includes all genders and ethnic groups as study participants and evaluates the overall data.

Larger sample sizes of women may often be required in comparison with sample sizes of men for several reasons. Increased variability attributable to cyclic hormonal fluctuations or other physiologic gender-based differences decreases the statistical power associated with a given sample size. Larger sample sizes or a longer followup time may also be required for studies with women than for comparable studies with men because certain outcomes of interest occur at a lower rate in women than in men. For example, the baseline rate of cardiovascular disease by age 60 in women is approximately one-third of that in men. Thus, the Physician's Health Study required a sample size of 22,000 men older than age 40 to detect a benefit of aspirin in the prevention of heart disease whereas the Women's Health Study required 40,000 women older than age 45 to detect the same result.⁴ Similarly, differences in disease prevalence among different racial and ethnic groups must be accounted for when determining sample size. In addition, when there is reason to expect racial or ethnic variation in biological or clinical responses, samples of minority women must be adequate to detect benefit and risk patterns that may be different from those in white women. The resultant increased sample size in studies involving women and minorities can increase the total cost of a study, which makes it critical that each research question and each study be as valid and efficiently implemented as possible.

METHODS OF RECRUITMENT AND RETENTION

Some of the potential barriers to recruitment and retention of women in clinical studies are unique. For example, women in general may have special economic or logistical barriers such as transportation or child-care difficulties that may prevent them from participating in a clinical study. Women from low socioeconomic groups or from rural areas may have additional economic or logistical barriers that do not necessarily apply to higher income or urban women. For any study that is to include these groups, investigators will have to make a substantial commitment to address these and other issues or barriers in every aspect of its design and conduct. The principal investigator or other collaborators may want to invite primary care physicians, whose practices often contain the target populations, to planning meetings to request their input regarding protocol design. Successful recruitment and retention can be enhanced by involving female research staff similar in race and ethnicity to the participants in the planning and conduct of the study and by designing recruitment materials and documents that are comprehensible and culturally sensitive.

In an effort to reduce barriers to recruitment, investigators may want to consider offering evening and weekend hours and providing child care, meals, and transportation. For further discussion on potential barriers to recruitment and how to overcome them see chapter 4: Participant and Community Issues in the Recruitment and Retention of Women in Clinical Studies.

Summary and Recommendations

When designing a clinical study, investigators must consider a number of issues, including the need to maintain the highest standards of scientific integrity and the balance between validity of findings and the ability to generalize research results to the relevant population groups. Key design issues include having a study population appropriate for the research question, various design and measurement issues, sample size, and recruitment and retention methods. Consideration of these issues results in a number of recommendations designed to:

- Determine gender representation in clinical studies based on the research question to be addressed and the base rates of the illness by sex or by rates of morbidity or mortality for the illness by sex.
- Incorporate extra visits and flexible scheduling needed by women into the study design.
- Increase support for studies into the issue of hormonal and other biologically driven, gender-based differences to determine the impact of these differences on drug and treatment responses.
- Conduct research on the social and psychological barriers to women's participation in clinical studies.
- Include the participant's own health care provider in the study, if possible, so that the bonding achieved in this relationship can be carried over to the research setting.
- Encourage meta-analyses and/or pooled analyses on existing data sets of women and minorities that are too small to be analyzed individually in an economical fashion.
- Ensure that all aspects of a study, from its planning through its execution, are sensitive to the cultural, linguistic, socioeconomic, and logistical characteristics of the populations studied. For example, this should include involving women and minorities in designing the research, in preparing study materials, and in interacting with participants in a culturally and linguistically sensitive manner.

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INVESTIGATOR AND INSTITUTIONAL ISSUES IN THE RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES

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Introduction

Although involving women in study populations presents many challenges for the institutions and investigators, the benefits to society of including them outweigh the associated costs.¹ However, the appropriate level of inclusion of women in clinical studies can only be achieved if investigators and their sponsoring institutions incorporate female participants' needs and concerns into their research planning decisions and work in partnership with women and men in the communities from which study populations are recruited. This should occur during the study design and planning phase, during outreach and recruitment efforts, and, most importantly, during the study itself. To be successful, these efforts must specifically address the barriers that prevent the recruitment and retention of women—especially rural, low-income, and minority women—in clinical studies.

An Overview of Clinical Studies

Before discussing the main issues faced by investigators and institutions in the recruitment and retention of women in clinical studies, it is useful to review the primary types of studies that exist and the concerns the patients and public have about these studies. Most clinical biomedical research takes place in the following general formats: randomized clinical or treatment trials, prevention trials, nonrandomized treatment trials, and observational studies. Each format presents investigators with different study design and implementation issues.

THE RANDOMIZED CLINICAL TRIAL

Treatment Trials

The prospective randomized study is the foundation of clinical research;^{1,2} it involves a considerable investment of time and money as well as patient and investigator efforts. With proper stratification, randomization can achieve an excellent balance between groups on variables that might otherwise introduce bias. The principal advantage of randomization is that it protects against the probability that a difference between comparison groups will be observed and declared significant when, in fact, the interventions or treatments being compared are equivalent and

the observed differences are due only to chance. Assuming adequate sample size, the randomized trial also protects against a conclusion that two interventions or treatments are equivalent when, in fact, one is superior. Randomized studies tend to reduce and even eliminate biased conclusions that might occur because of subjective factors that may influence research results, for example, patients want to get better and investigators want successful results, or patients or investigators may believe one treatment is superior to another.³

Perhaps the most serious potential objections to randomized studies center around ethical issues,^{4,5,6,7} for example, the decision to withhold treatment from a control group or to give a possibly inferior treatment to one group. The random allocation of patients in a well-designed clinical study is more ethical than trying out a new therapy in an unscientific manner or basing treatment on clinical impressions or past experience.¹ It has been argued that researchers have an obligation to use their judgment and recommend the “best” therapy, no matter how tentative or inconclusive the data on which that judgment is based.⁸ However, problems arise when there is both uncertainty about the value of a new therapy and doubt regarding the efficacy of standard treatment.

The researcher involved in a randomized study makes a scientifically valid judgment that the best therapy is not known. Many physicians, however, have difficulty admitting to the patient or convincing the patient that they do not know what the best available therapy is. A leading cause for failure to enter a patient in a clinical study, when an appropriate study is available, is physician choice.⁹ If certain types of patients are systematically excluded, this can result in selection bias and reduce the ability to generalize research results even when the study is internally valid.¹⁰

The attitudes of patients and the public in general toward clinical studies have been evaluated by Cassileth, et al. in a survey of 295 subjects.¹¹ Most respondents, 71 percent, believed that patients should serve as research subjects and that such patients make an important contribution to society. However, a substantial minority, 29 percent, disapproved of patients serving as research subjects, and 36 percent thought that patients receiving treatment recommended by their physician received better care. Of interest is that 70 percent of respondents thought that their doctors knew privately which of the investigational treatments was best. Ganz’ summary of the concerns of patients and the public regarding clinical studies is shown in table 1.¹²

TABLE 1—CONCERNS OF PATIENTS AND THE PUBLIC

- Do patients entered into clinical studies receive the best medical care?
- If physicians would not agree to participate in a clinical study, should patients be expected to participate?
- How can patients (and their physicians) be assured that clinical studies are well designed and will answer important questions?
- Can better methods be developed to inform patients about treatment options?
- How can patients obtain more information about survival, treatment, toxicity, and quality-of-life before considering participation in a clinical study?
- Is disease-free survival an acceptable outcome measure for clinical studies?

SOURCE: Ganz P. Clinical trials: concerns of the patient and the public. *Cancer* 1990;65:2394-99.

For human subjects who volunteer to participate in clinical studies, the ultimate protection against the conduct of an unethical study is an intelligent, informed, conscientious, compassionate, and responsible investigator.¹³ Institutional review mechanisms or elaborately designed consent forms¹⁴ are not foolproof means for avoiding ethical problems. Four community models have been established to make it possible for patients who are treated in smaller communities to be included in national clinical trial protocols.¹⁵

- **The Medical System—Participation Model.** In this model, researchers bring health care professionals practicing in the community into the research network. One mechanism for attracting participants is to have local physicians enroll women in studies and follow them to detect possible side effects from an experimental drug.
- **The Medical System—Referral Model.** In this model, representatives of the research organization ask local practicing professionals to recruit patients and refer them to a central network. In this case, the investigators and support staff work totally within established research organizations.
- **The General Community—Direct Model.** In this model, the central research organization appeals directly to community residents, often using familiar media sources.
- **General Community—Indirect Model.** In this model, representatives of the research organization mobilize institutions to serve as intermediaries between community residents and their organization. For example,

a network of outpatient clinic facilities might be used to attract patients of a specific ethnic group. These clinics perform the research with the sponsoring institution acting as the partner with monitoring responsibilities. Considerable organizational expertise is required for mobilizing community members, leaders, and representatives of institutions to participate directly in research. This approach implies that there is a preexisting infrastructure for identifying community leaders and mobilizing community resources.

PREVENTION TRIALS

The factors motivating an individual to participate in a disease prevention study such as a chemoprevention study for breast or prostate cancer include the following:

- Feelings of altruism that the study may ultimately help someone else.
- An individual's perceived risk of developing the disease.
- The severity of the disease to be prevented.
- Personal or cultural attitudes toward the disease to be prevented (e.g., a fatalistic attitude toward cancer).
- The perceived efficacy of the proposed intervention.
- The perceived risk of the intervention.
- An understanding of randomization and the nature of controlled, especially placebo-controlled, studies.
- An understanding that there may be no personal gain, only a gain in medical knowledge.

Another motivating issue that is similar to those for treatment studies is trust in the investigator that she or he will not place the subject at unnecessary risk.

The issue of perceived risk is exceedingly important to prevention studies. If an individual feels that she or he is at minimal or no risk for the development of a given disease, there is no motivation for participation in a prevention study. Currently, there is no established instrument to measure perceived risk, but attempts are being made to identify one.^{16,17} An individual's perceived risk of cancer, for example, is dependent on her or his experiences with cancer in family, friends, and acquaintances as well as on her or his understanding of cancer risk factors. Women who are at low risk but perceive themselves to be at high risk often volunteer for clinical trials, whereas women who are at high risk but perceive themselves to be at low risk do not volunteer. Because prevention studies involve healthy individuals who are at risk but have not yet developed the disease in question, the proposed intervention must be essentially devoid of

side effects. This situation differs markedly from the situation of an individual being treated for a life-threatening disease who is willing to tolerate undesirable and prolonged side effects. For the research subject on a prevention study to be compliant with long-term treatment and followup, she or he should experience only minor, if any, side effects.

Trust in the investigator is a major issue in any clinical study and lack of trust is a potential barrier to participation.¹⁸ The issue of trust is dependent upon the subject's prior experience with health care providers and the reputation of the investigator or institution performing the study. Long-lasting recollections and concerns, especially among African Americans, regarding the Tuskegee syphilis study¹⁹ in which appropriate treatment for the disease was withheld from the African-American men participating in the study should not be underestimated.

These concerns and how they can be addressed by investigators and institutions can be clustered into the following issue categories presented in the next section. To be successful, the investigator and the sponsoring institution must be sensitive to all of these issues and work closely to establish a partnership with the subject and her or his supportive care system. Attempts to use the models described above are now being used to recruit healthy participants into prevention trials.

NONRANDOMIZED TREATMENT TRIALS

Although the principal aim of treatment studies is research, they also promote improved patient care and contribute to the professional education of health care providers.²⁰ Well-designed treatment studies, in general, offer more than just state-of-the-art care; they are the best available treatment. The public, in general, is currently more aware of the value of treatment studies than of other types of studies. Cancer patients, in particular, are seeking physicians and medical institutions that participate in National Cancer Institute (NCI)-approved clinical studies.

The factors motivating an individual to participate in a treatment study are complex. Individuals with advanced, life-threatening diseases such as cancer and AIDS are, as a rule, highly motivated to participate in clinical studies because cutting-edge treatment offers them greater hope of benefit than standard treatment. As noted by one researcher, "The miserable have no other medicine . . . only hope."²¹ This knowledge places an even greater responsibility on the investigator who may be interacting with a potentially vulnerable class of patients. These patients often wish to try all options in an attempt to hold on until a "cure" is found.²²

Kardinal and Cupper evaluated 50 patients with advanced cancer who were being treated in NCI-approved clinical studies²³ and found that there were three primary factors motivating them to participate:

- Hope that the new treatment offered a better chance for control of their disease.
- Altruistic feelings that, even if the treatment does not help them, it might ultimately help others. As stated by a young man with acute leukemia, “I’m glad to be on it. I have to be . . . for the men coming after me.”
- Trust that the physician would not have recommended an investigational therapy unless she or he thought it would help. It is this issue of trust that places enormous responsibility on the physician investigator.²⁴

Kardinal and Cupper also noted that some patients with advanced cancer feel trapped by a lack of therapeutic alternatives. Some of their views are summarized in the following statements: “What option do I have?” “I know what I have and I can’t shake it.” “There is a chance that this might really help.” However, by participating in a study even people who feel trapped show improved morale and an increased sense of purpose. Because patients with AIDS or cancer are forced to confront a number of issues, including their own mortality, that are not applicable to individuals with less-immediate life-threatening diseases,²⁵ their rights and welfare must be especially safeguarded.

OBSERVATIONAL STUDIES

Observational studies differ in several important respects from other types of clinical studies, but they have provided many unique and valuable insights into the causes and development of major diseases. For example, one of the major contributions of the Multiple Risk Factor Intervention Trial (MRFIT) was the development of stable estimates of relative and absolute risk for coronary heart disease in men based on their levels of serum cholesterol. These estimates, which have been critically important in formulating national guidelines on cholesterol-lowering measures, were not based on data generated during the MRFIT trial itself but on observational data generated on the large group of men screened for participation in MRFIT.

In observational studies, a nonrandomized population is followed for a period of time. Baseline and followup physical examinations are conducted and laboratory samples taken. The data generated permit researchers to identify and test hypotheses with regard to the etiology and development of disease, to develop estimates of comparative risk among population subgroups, and to refine and improve the objectives and design of other types of clinical studies.

Many of the strengths of observational studies lie in the ways that they can complement other types of clinical studies. For example, only a small number of intervention arms are possible in randomized, controlled studies. Results from such studies will not yield direct information on other interventions that are similar to, but not the same as, the interventions studied. An observational study, on the other hand, can collect a broad base of data that may shed light on a range of interventions.

Major randomized clinical studies require that many potential participants be screened in order to recruit the targeted number of actual participants. This group can provide a population for an observational study at a relatively modest additional cost. This is the case for the NIH’s Women’s Health Initiative, which plans to enroll 63,000 women in a randomized clinical study and an additional 100,000 women in a complementary observational study.

The significant size of the population enrolled in this observational study will also allow researchers to collect data across a spectrum of racial and ethnic minority groups, thus increasing the chances of identifying and understanding disease risk factors in individual minority groups.

For many individuals, an observational study provides an opportunity to participate in an ongoing and potentially valuable research effort without having to undergo potentially undesirable treatments or interventions. Other individuals may be able to participate in an observational study even though they are ineligible for participation in a prevention or treatment study.

Key Investigator and Institutional Issues

COST AND INSURANCE ISSUES

The high costs of conducting clinical studies may render any additional costs associated with the inclusion of women or minorities in clinical studies excessive in the perceptions of many investigators or research administrators. These high costs are inherent in the nature of the research and are increasing due to current research trends.

Clinical investigators have responsibilities associated with research in humans that do not apply to either the work effort or budget of basic science studies; these responsibilities exist whether participants are ill or healthy. Increasingly, studies involving humans are designed to measure incremental benefit, or the additional benefits of a “new” treatment over the benefits of the best current available treatment. These additional benefits may be minor and are more often related to functioning and quality-of-life than to survival. As the increments of

improvement become smaller, increasing numbers of investigators are turning their attention to research on primary prevention of disease and its preclinical detection and management. In the areas of preclinical detection and management, large numbers of participants are needed to measure success, which leads to an increase in the numbers of multicenter, randomized studies.

An additional cost factor faced by investigators and their institutions in including women in clinical research is the lack of insurance to cover untoward events that may affect study subjects. Historically, the costs of the side effects of therapeutic studies have been paid for by third-party, personal, organizational, or study-specific liability insurance arrangements. Liability associated with primary prevention studies has been traditionally covered either by specifically designated public funds, as a direct research cost or as a specifically insured research cost. As clinical scientists have begun to solicit individuals who are not their clients to volunteer as study subjects, designating who will pay the costs of therapeutic and primary prevention studies has become more difficult. As a result, many subjects may be deterred from participating because they have no assurance that treatment for possible costly side effects will be covered. Furthermore, the lack of insurance coverage for participants may make researchers and their institutions, already lacking adequate resources, liable for the costs of research-associated side effects.

Even for treatment studies in which costs could potentially be covered under routine patient care and for studies in which treatment is considered experimental, costs may not be reimbursable. This factor may lead to marked underrepresentation of low-income women in clinical studies. Thus, in some cases, patients who wish to enroll in studies of lifesaving treatments cannot afford to participate unless investigators can cover their costs.

STUDY DESIGN AND RESEARCH STAFFING ISSUES

In designing studies to include female participants, researchers should carefully analyze the goals and purposes of the study to identify gender-specific issues. Once researchers identify these issues, they should develop solutions applicable to a broad range of subject needs and situations. Employing women in visible, key positions during the strategic planning process helps to ensure that these solutions will be viable; it can also serve as an aide to recruitment.

Because of the large number of subjects required, most randomized studies of major diseases require multicenter and multidisciplinary collaboration. The attention given to the selection and recruitment of collaborating centers and investigators is critical, as is the careful definition of the

number and qualifications of eligible subjects. The experience of research centers and whether they have adequate systems for participant data collection and management are important considerations in the assessment of community resources. The evaluation of these factors also helps to determine whether the research design should be centralized and carried out from a single research facility or decentralized and carried out in community centers.

The success of some networks designed to bring community hospitals and clinics, their health care professionals, and their patients into cancer chemotherapeutic studies has led to their involvement in chemoprevention preclinical detection and management studies. These networks have been required to join with a research center and have usually chosen to link-up with one or more designated groups of institutions committed to multicenter studies. There has been a serious effort to include cancer prevention and control research in these networks. For this reason, researchers should consider addressing not only existing networks but also newly created or ad hoc alliances among existing networks, institutions within those networks, or outside organizations.

ISSUES RELATED TO INSTITUTIONAL REVIEW BOARDS AND THE PERSPECTIVES OF POTENTIAL STUDY PARTICIPANTS

In 1973, NIH established an Office for the Protection from Research Risks, which mandated Institutional Review Boards (IRBs) in each institution receiving Federal research funding.²⁶ The primary purpose of these IRBs is to ensure that researchers are aware of the rights and well-being of study subjects in clinical research projects. Among the few initial rules promulgated by the IRBs was the mandate requiring that the research designs include an “equitable selection of subjects.”

Members of IRBs review research protocols before granting funds to researchers. The boards require that investigators provide justification for single-gender selection and for populations selected. However, it is not until the annual or interim project review that the board actually learns the composition of the study population; this procedure limits the ability of an IRB to ensure a balanced study population before research begins. Despite recent efforts of IRBs to encourage diversity in study populations, researchers tend to choose subjects from the most convenient subject population. If asked to account for a lack of diversity, they often indicate that the effort made to recruit other than mostly middle-class male subjects was unsuccessful.

In addition to the responsibility for ensuring the appropriate diversity among study subjects, IRBs are also charged with establishing a communication framework to answer participants' questions about the studies.

Although answering questions on potential side effects in ways that study participants can understand may require extra effort from investigators, the benefits of this in terms of enhanced trust and cooperation from participants are unmistakable in general and may be particularly salient for women in groups heretofore excluded from research, less trusting of researchers, or less experienced with the research environment.

At times, investigators may be responsible for screening individuals whose participation may not be in their own best interest or in the interest of the study. For example, an individual may perceive herself or himself to be at high risk for a disease and consider volunteering for a study when, in fact, the information obtained does not indicate that she or he faces such risk. This is often the case among young women who volunteer to participate in breast cancer studies. Investigators may be tempted to enroll these individuals because they are anxious to participate and will comply with study requirements. However, investigators must not capitalize on these individuals' perceptions of personal risk but should decide whether such participation makes a valid contribution to the study.²⁷

ISSUES RELATED TO RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES

Although experience from studies such as the National Heart, Lung, and Blood Institute's (NHLBI's) Pawtucket Heart Health Program (PHHP) shows that, in general, women, including older women, are responsive study participants,²⁸ a majority of clinical investigators are inexperienced in the use of strategies to recruit patients who do not present through the usual channels, particularly women of diverse racial and ethnic groups and socioeconomic strata.

Most urban universities have not yet fully reached minority communities to educate them on the personal and societal benefits of participating in clinical research. Time-consuming and costly targeted recruitment strategies often have to be added to population- or network-based recruitment to ensure that diverse populations are reached. Recruitment yields in special populations may be less than the 3 to 15 percent reported in clinical studies and the 1 to 2 percent reported in primary prevention studies.²⁹ This means that 85 percent or more of the researchers' community recruitment activities are nonproductive; unfortunately, such nonproductive activity is not usually budgeted.

Each special population requires a recruitment strategy customized to its characteristics and concerns. The more customized the targeted strategies, the more additional resources have to be planned and budgeted. Time commitments required from staff also increase markedly when targeted recruitment strategies are used. In the case of

identifying high-risk women, additional staff time is needed to review pathology records. Additional outreach recruiters may also be required when researchers who have limited familiarity with the cultures or languages of ethnically diverse populations are attempting to recruit those populations for a clinical research study.

Effective recruitment may also require the development of partnerships between research organizations and their target groups. The ability to develop partnerships is central to the successful planning of the recruitment and retention of women in clinical prevention studies. There are two basic types of partnerships:

- **Partnerships With Individuals.** Forming partnerships with individuals or volunteers who help to recruit additional women into studies is a cost-effective way to increase participation rates.³⁰ The volunteers' awareness and knowledge of the cultural environment can provide credibility and access for the research team. Because they are often members of targeted social networks, volunteers help foster local awareness while acting as full-time agents for information dissemination. This partnership also helps promote study retention and institutionalization of programs after funding ends.
- **Partnerships With Organizations.** Partnerships with representatives or agents of organizations may be more difficult to foster than partnerships with individuals. Organizations must be approached carefully through gatekeepers or decisionmakers. The goals and needs of the organization must always be respected and accountability criteria such as profit, reputation, and prestige openly discussed.

The Columbia River Clinical Community Oncology Program in Portland, Oregon, provides one example of the successful recruitment and retention of women in clinical studies using partnerships and networks. The program involves members of the Urban League and the American Cancer Society Underserved Committee. Researchers in the program have formed a liaison with the AIDS Research Network and the National Black Leadership Initiative. Women's church groups in the African-American community also have been contacted. Contact with these groups has led to the development of a list of community leaders; leaders who appear on several lists are considered as potential research recruitment agents. Recent activities using leaders from the community have helped to identify battered women as potential participants in cancer research.

Establishing an advisory committee or coalition comprised of a wide range of groups to participate in the initial planning of the study and to function as an integral component of the study as it develops is an important component in successful recruitment and retention of special populations. The committees or coalitions are

able to assist with study design and act as endorsers. The coalition should be comprised of a wide range of organizations and their representatives, including public agencies, health care providers, senior citizens' groups, worksite managers, families, and spiritual and/or religious organizations. There are many other possible sources for participants as well; for example, social clubs may provide investigators with access to women of differing ethnic backgrounds; professional organizations provide access to women in health-related, education, business, or other fields; housing or tenant associations provide access to specific neighborhoods, subsidized populations, or elderly persons. Finally, voluntary and professional organizations such as the National Cancer Society, the American Heart Association, the American Psychological Association, the National Medical Association, and many others can be essential in forming a coalition.

Study visibility is one of the most reliable indicators of what the level of participation will be. Large-scale, low-budget public relations campaigns reach community members, especially those who have no affiliation with community organizations, in the environments they frequent the most. Efforts to reach the public in these different environments may include, for example, placing posters in a grocery store or public service announcements on the television or radio. Learning about a study through a familiar information source may lend credibility to a project.

Benefits and Risks to Investigators in Conducting Clinical Studies

Involving women in clinical studies can augment the career development and general benefits that accrue from involvement in clinical research for the investigator and her or his institution. There may be special incentives for involving women in clinical trials until the historical underrepresentation of women and the relative neglect of the disorders affecting them has been rectified. Furthermore, some sectors of the public perceive clinical research as producing great social benefit and this positive perception carries over to sponsoring institutions.

No specific risks, except the historical concerns regarding research with women of childbearing potential, apply to clinical studies that include female subjects. However, all clinical investigators assume general risks. Perhaps the greatest risk to investigators and their sponsoring institutions is that their research will not answer important questions. Thus, researchers must avoid any distraction from the pursuit of high-quality research, including the temptation to conduct easily fundable research or research

with less than optimum designs. Inappropriate specification of a study design, with respect to addressing gender and diversity issues, would fall into this category. The lack of insurance coverage for the untoward events affecting clinical study subjects, discussed earlier in this chapter, is another major risk for investigators and institutions. Finally, the additional burdens placed on researchers in clinical settings as opposed to basic research settings may be regarded as a risk. For example, investigators are required to provide detailed explanations of research protocols, risks, and benefits to participants. They must also respond to unanticipated health-related and personal events in participants' lives. Meeting these demands reduces productivity and places clinical investigators at a special risk in the academic environment.

Summary and Recommendations

Each of the major approaches used in biomedical research—randomized clinical or treatment trials and nonrandomized treatment studies, prevention trials, and observational studies—presents a different set of study design and implementation challenges. Other issues considered in this chapter cut across all types of clinical research. These issues include cost and insurance reimbursement, research study staffing, and collaborative networking, IRBs and the perspectives of potential study participants, and recruitment and retention strategies. Recommendations related to these issues are to:

- Resolve the issue of lack of insurance coverage for treatment of incidental medical conditions and research-associated side effects to promote the inclusion of women in clinical studies.
- Analyze the goals and purposes of clinical studies to identify issues of particular relevance to women.
- Include women in the strategic planning process and employ them in visible, key positions, whenever possible.
- Plan and establish infrastructure to support both multicenter and community-based disease treatment and prevention studies, and use current exploratory models to develop estimates of the dimensions, performance, and utility of proposed future networks.
- Make efforts to capture, analyze, and evaluate information on the process of establishing and maintaining research partnerships.
- Expand the role of IRBs to encompass research funded by non-Federal agencies and the ongoing process of research.

- Involve IRBs in the early design phases of research to ensure that there is an equitable blend of study subjects.
- Ensure that all participants' questions about the study and possible side effects of treatment are answered fully and comprehensibly; avoid even subtle intimidation of study participants.
- Develop cost-effective recruitment approaches that combine strategies targeted toward involving women as a group as well as women of a particular race, socioeconomic status, age, risk profile, or geographic location.
- Encourage partnerships and networks, which are excellent methods for recruitment of diverse female populations, and disseminate information about successful recruitment strategies such as screening, counseling, and referral events (SCOREs), which were developed for the Pawtucket Heart Health Program.^{31,32}

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PARTICIPANT AND COMMUNITY ISSUES IN THE RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES

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Introduction

Federal and state governments, researchers, and institutions have expressed an increasing interest in recruiting women into clinical studies. However, the road to meeting that goal is paved with challenges. The needs, attitudes, and beliefs of women, including minority women and women from low socioeconomic strata, must be examined if they are to be effectively recruited and retained for clinical research. Studies have suggested that the underrepresentation of women in clinical studies is probably related to multiple factors.¹ Access to health care, mistrust of the medical system, language barriers, cultural beliefs, and even transportation and child care are all issues that must be addressed to ensure that women are able and willing to participate in clinical studies.² These cultural, social, and economic voids may serve as barriers between research organizations and the patient populations they are intended to serve.

The studies that have been most successful in recruiting and retaining women have used a variety of strategies. Examples of some of these successful recruitment strategies are described in chapter 5: Current Experiences in Women's Health Research. Community partnerships, spiritual and religious leaders, and support networks can all play a role in reaching women of heterogeneous backgrounds, lifestyles, and occupations. In addition, the media, through public service announcements, health programs, and printed materials, can do much to establish trust relationships and inform women about health issues.

Key Issues

ISSUES IN THE BELIEFS AND ATTITUDES OF WOMEN

Understanding perceptions, beliefs, and attitudes is critical if women from specific populations targeted for study are to be successfully recruited. Misinformation, suspicion, or distrust among potential study participants regarding clinical studies, the medical profession, and research team members can greatly diminish the success of patient enrollment efforts.

Though the body of research on patient attitudes is still limited, the existence of such reservations about participation in clinical studies in certain populations has been suggested by the findings of several studies conducted in the United States and Europe.² The patients who most readily elect to participate in clinical studies

may not always come from the populations most in need of study. Actual study participants tend to be young and well educated.²

Participants' opinions about the quality of study design and confidence in those conducting the research can be important determinants of enrollment and retention. The history of women's medical treatment has also influenced their perceptions of the health care establishment and of the long-term safety of some treatments. Reports of medical treatments with adverse effects, for example, therapies with thalidomide and DES, have also diminished many women's trust in the research community. The experiences of members of minority communities, who may not have adequate access to or availability of affordable services because they lack or have insufficient health insurance, only reinforce such perceptions. For example, the Tuskegee³ experiment, conducted on poor, rural black men, is the basis for mistrust of research within this group in particular.

This sense of mistrust has been aggravated by women's perceptions of a male medical establishment that is insensitive to their needs and concerns.⁴ Such perceptions may be hard to dispel when clinical studies are designed and conducted primarily by white males. Historically, only a small percentage of health and research team personnel have been minorities and women.

Another factor limiting the willingness of many women to participate in a clinical study may be a lack of knowledge about health and disease issues and about clinical studies in general. Denial of the presence and dangers of a suspected illness can compound a reluctance to participate; this is a problem experienced by many women of diverse backgrounds. Other barriers, for example, a sense of fatalism or of yielding to inevitable external forces, may be more characteristic of certain populations or socioeconomic groups. Researchers have found this to be prevalent, for example, among Hispanics, and it can prevent the entry of Hispanic women into clinical trials.⁵ In addition, when the husband is the sole decisionmaker it is also less likely that the woman in the family will participate in a clinical trial. Lastly, concerns about confidentiality can impede the enrollment of many women. For example, women may fear that their human immunodeficiency virus (HIV) status will become known to family or friends if they participate in a clinical trial.

A number of strategies have been explored to overcome the reluctance felt by many women to participate in clinical studies. In the African-American community, for example, researchers have found church-based outreach programs effective in building strong, long-lasting relationships that have created trust. Among those who attend African-American churches, 85 percent are women at midlife or older.⁶ Church-based outreach programs are exemplified

by the joint programs of the Congress of National Black Churches (CNBC) for health-related education in conjunction with research institutions. The CNBC has successfully collaborated with George Washington University and Howard University in developing education programs for the African-American community in the metropolitan Washington, D.C., area, including programs on lipid research, heart disease in women, and health issues for youth and families.⁶ Similar advantages can be gained by hiring influential members of the study population to recruit participants. We recommend that the following steps be taken:

- Nurture positive attitudes and beliefs by establishing and maintaining, whenever possible, one-on-one relationships that foster trust and respect between research staff and study participants.
- Include women in clinical trial staffs, particularly women of the same ethnic or racial origins as those in the study population, to the greatest extent possible.
- Promote joint decisionmaking and informed consent to the maximum extent possible so that participants are empowered to become active participants in their own treatment.
- Encourage interactions and facilitate the establishment of educational and support networks between former and current study participants to help support positive attitudes.

ISSUES IN SOCIOECONOMIC STATUS

Frequently, the effects of low income correlate strongly with a disproportionate burden of disease. In many populations, lower income levels are often accompanied by lower levels of education, literacy, and employment. Substandard housing and environments threatened by violence and substance abuse are also common among members of lower socioeconomic groups.

Women of low socioeconomic strata, particularly those who serve as caregivers, have extremely limited time and financial resources to invest in clinical study participation. Child care and food costs associated with participation in a study as well as an inability or unwillingness to take time off from a job can preclude their enrollment. The mobile lifestyles of other populations, for example, migrant workers and the homeless, present additional barriers to participation. Principal investigators who are unfamiliar with these lifestyles must make special efforts to understand these barriers and overcome them if these groups are to be successfully recruited and retained. We recommend that the following steps be taken:

- Make participation in clinical studies possible for women, regardless of their ability to pay. The use

of financial incentives, without creating an undue influence, is an appropriate recruitment tool.

- Adapt program designs that overcome the barriers to women's participation, particularly minority women and women from low socioeconomic strata. Examples of such actions include maintaining extended and flexible study clinic hours, providing transportation and child care, and developing study materials that are culturally and linguistically appropriate.

ISSUES IN INFORMATION DISSEMINATION AND COMMUNICATIONS

Clinical study designers and staff face great challenges in communicating a basic understanding and awareness of particular research opportunities. As mentioned above, educational, economic, and geographic factors can weigh heavily on the abilities of individuals in target populations to receive and understand the necessary information.

Physician referrals are a crucial element in the successful recruitment of a study population, but many physicians and other health care providers, including women and minority health care providers, are either unaware of clinical trials or do not adequately encourage qualified patients to participate in research projects.

For many populations, limited language skills can affect communication and outreach efforts of clinical programs. Researchers and others who develop communication strategies must take careful account of target populations' primary language or dialects, use of slang, and literacy levels. Alternative learning styles must also be accommodated. Since their first use in 1975 by the NHLBI for its Coronary Primary Preventive Trial (CPPT),⁷ media-based recruitment campaigns with specially designed communications and education strategies have proven to be a cost-effective method for recruiting subjects for clinical trials.

The "Cuidando Su Salud" radio program on Radio Borinquen (WILC-AM 90) in the metropolitan Washington, D.C., area provides an example of effective media outreach to minority populations. The program, produced by Elmer E. Huerta, M.D., M.P.H., targets Spanish-speaking audiences with messages and discussions about current health topics, including screening for cancer and AIDS and tobacco use prevention messages; the program also reassures the audience about the confidentiality of their enrollment in preventive health programs. The daily program reaches an estimated audience of 75,000 people. Since it began in 1989, it has had a measurable impact on the number of women seeking local services for mammograms and Pap smears.

For certain populations, which are geographically isolated or experience high rates of poverty, mass media alone may not always be effective. For these populations, distributing flyers through Federal aid programs, for

example, Food Stamps or Social Security, can help.

In one example, the Hawaiian study Malama Na Wahine Hapai: Caring for Pregnant Women⁸, interpersonal communications were the key elements for patient recruitment. The Changing Asthma Through Social Support program of the St. Louis Neighborhood Asthma Coalition¹ relied on trained neighborhood residents who gave asthma management presentations and served as case workers for children enrolled in the program. The program enrolled 300 children in study neighborhoods and another 300 in comparable control neighborhoods. Initial enrollment was primarily accomplished through personal contacts with the participants' mothers, based on information received from emergency room and asthma clinic records. We recommend that the following steps be taken:

- Plan carefully, select communications channels judiciously, and pretest thoroughly before launching recruitment efforts. Followup is also essential and should include solicitation of feedback and evaluation of program effectiveness.
- Rely on multiple channels for communications and outreach to health professionals from many disciplines to assist in the recruitment of study populations.
- Develop media outreach strategies with spokespersons who can serve as role models and emphasize ethnically targeted messages, when appropriate.
- Use informal communication networks to promote enrollment and compliance with clinical protocols.
- In all outreach efforts, adapt the language of science to the needs of patient groups. Make efforts to accommodate alternative ways of learning, including the use of low-literacy materials.

ISSUES IN ACCESS TO SERVICES

As discussed above, the responsibilities frequently assumed by women as caregivers and providers for children, spouses, and parents leave little time or room for participation in clinical trials. Often, practical and logistical problems can present the greatest barriers. For example, women with disabilities may have great difficulty in accessing basic health care services, much less a specialized clinical research study.

Geographic isolation can result in limited awareness of available services and clinical study opportunities. In rural settings, lack of transportation and distantly located research centers can present the greatest barriers to both recruitment and retention, particularly for women from low socioeconomic strata.

Barriers to research opportunities can also reflect poor access to health care. The lack of a primary care provider or other source of health care and/or a lack of health

insurance are major reasons for poor health care. A survey whose findings were recently issued by the Commonwealth Fund of New York found that more than one-third of the women surveyed said they lacked basic, preventive services during the past year, largely because of high costs and gaps in insurance.⁹ Among women who have some form of insurance, exclusions of coverage for clinical studies are common and create a financial barrier to enrollment.

Some populations face additional barriers in accessing health services, including clinical trials, because of differential treatment. Lesbian women, for example, have traditionally experienced misunderstanding and even hostility on the part of health care providers, particularly in communities in which this type of life style is unfamiliar.¹⁰ Studies have also shown that perceptions of differential treatment held by lesbian women have led them to fear receiving inferior care because of their sexual orientation. With respect to clinical studies, fears about confidentiality breaches, unequal treatment, and biases by study staff can seriously impede enrollment of lesbian women, particularly as they grow older.

Finally, lack of U.S. citizenship, fear of confidentiality breaches with respect to immigration status, and possible deportation are important barriers for immigrant groups. We recommend that the following steps be taken:

- Conduct community consultation and proper staff training to accommodate the special needs of study populations when designing clinical studies.
- Provide access to health research programs and facilities for women to the fullest extent possible, including transportation services.
- Enhance participant retention by developing flexible schedules at study sites, providing alternative service delivery such as the use of at-home examinations, offering complete medical insurance coverage for study participation, and providing day-care services.
- Establish and use role models and advisory boards from the community to help direct programs. Use community confidants to help engender a sense of trust and guarantee of confidentiality.

ISSUES IN COMMUNITY RELATIONSHIPS

A central element in nearly every barrier to recruitment and retention of participants in clinical studies, particularly recruitment and retention of minority women and women from low socioeconomic strata, is the nature of the relationship between research institutions and the communities whose populations they target for clinical study participation. In the absence of common goals or a shared recognition of the unique needs of the community,

clinical studies cannot successfully coexist with a community. The development of partnerships with concerned members and representatives of communities is a critical element for successful recruitment and retention. These partnerships must be based on a foundation of trust and mutual respect among the research institution, community leaders, and study candidates.

Effective partnerships not only engender broad community support and successful study participation but also result in a number of additional, tangible benefits to all concerned. Such partnerships foster strong personal relationships between study subjects and clinical staff that ensure good patient retention and compliance with study protocols. In the words of one cancer patient, "I still consider my research nurse to be one of my best friends. There is a definite need for continuity in the health care profession to bring about a feeling of trust."¹¹ The partnerships also help ensure that study protocols and recruitment methods are culturally sensitive. Studies benefit from hiring program staff who reflect the ethnic and racial composition of the populations being studied, but benefits accrue beyond the core study staff to participating volunteers and community staff who gain marketable skills and training.

Finally, the broad community support and participation that result from successful partnerships can also produce beneficial secondary effects such as greater community interest in the sciences, stable employment opportunities, and greater community activism. We recommend that the following steps be taken:

- Capitalize on the success of community partnerships in meeting recruitment and retention goals by initiating the partnerships early in the planning process.
- Identify representatives of broad-based groups, including spiritual, religious, and business leaders, to participate in partnerships with the research institution.
- Use research team members with similar racial, ethnic, and language backgrounds as the potential study participants. Whenever possible employ women and minorities as principal investigators and educators to help inspire a greater sense of trust among female study participants.
- Address sensitivity to gender, racial, and ethnic issues during research training. Stress the importance of developing mutual confidence between study participants and research staff and the importance of patient responsibility and decisionmaking skills.
- Inform patients of findings of the protocol to the fullest extent possible by openly discussing the treatments and their implications.

ISSUES IN SOCIAL SUPPORT SYSTEMS

The availability of social support systems such as group counseling or the use of confidants positively influences health behavior outcomes for all patients. Studies have linked the availability of “confidants” to individuals undergoing stress as an important factor in reducing depression.¹² Other studies have suggested a possible link between social support and certain measures of immune response and the improvement of health status.¹²

Traditional methods of designing and conducting studies have not always recognized the importance of social support systems as communications channels and as important mechanisms for the health and support of patients. For women in particular, the integration of social support systems into study design may be an important element in successful recruitment and retention. These social support systems may play an especially important role in helping women to cope with treatment-related stress that occurs during a study. In studies on smoking cessation, for example, researchers have found women to be more attuned to and better able to use social support than men.¹² In a randomized study of 66 female and male smokers, investigators found that women were more responsive to clinic therapy that stressed social support.¹³ Adequate social support may also be of greater importance for certain populations of women who traditionally rely on networks of extended relatives and informal networks, including church- and neighborhood-based groups. We recommend that the following steps be taken:

- Incorporate formal and informal sources of social support into the design and conduct of studies by developing cooperation between clinical study programs and communities.
- Work with existing community structures such as church groups that can help make patients aware of clinical studies and help them cope with treatments once the study is initiated. Informal networks can be accessed through formal community structures.

ISSUES OF DATA AVAILABILITY AND TARGETING OF SPECIAL POPULATIONS

Medical interventions in certain populations are hindered by a lack of knowledge about the incidence and prevalence of disease and about health service utilization. For example, studies on Native Americans can present a challenge because health data in general, and especially for some tribal groups, do not exist or are limited. These challenges are compounded when formal health services are undeveloped within tribal communities, particularly in rural areas.

Lesbian women also present a challenge to investigators. Historically, lesbians have been alienated from health care systems because of negative or hostile attitudes expressed by providers.¹⁰ Consequently, there are inadequate data about this population, although some of the data do suggest that there may be important differences in several health parameters between lesbians and heterosexual women. Efforts to identify and/or recruit lesbians for participation in clinical studies require specially crafted research tools. We recommend that the following steps be taken:

- Make the best use of all available community sources of data when studying poorly documented populations.
- Include information on cultural, racial, and behavioral characteristics when defining special populations.
- Make the fullest use of clinics, advisory boards, and other resources that serve a target special population; they have the ability to provide needed data about that group and can provide assistance in recruiting study participants.

Summary and Recommendations

In order to successfully recruit and retain women in clinical studies, particularly minority women and women from low socioeconomic strata, investigators and staff must examine and understand the needs, attitudes, and beliefs that raise barriers to participation. Sensitivity to the constraints placed on women by poverty, family responsibilities, experience with the health care system, language limitations, and limited access to health care services must be a hallmark of efforts to recruit and retain women. We recommend that the following efforts be made:

- Nurture positive attitudes and beliefs by establishing and maintaining, whenever possible, one-on-one relationships that foster mutual trust and respect between research staff and study participants.
- Include women in clinical trial staffs, particularly women of the same ethnic or racial origins as those in the study population, to the greatest extent possible.
- Promote joint decisionmaking and informed consent to the maximum extent possible so that participants are empowered to become active participants in their own treatment.
- Encourage interactions and facilitate the establishment of educational and support networks between former and current study participants to help support positive attitudes.

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- Make participation in clinical studies possible for women, regardless of their ability to pay. The use of financial incentives, without creating an undue influence, is an appropriate recruitment tool.
 - Adapt program designs to overcome the barriers to women's participation, particularly minority women and women from low socioeconomic strata. Examples of such actions include maintaining extended and flexible study clinic hours, providing transportation and child care, and developing study materials that are culturally and linguistically appropriate.
 - Plan carefully, select communications channels judiciously, and pretest thoroughly before launching recruitment efforts. Followup is also essential and should include solicitation of feedback and evaluation of program effectiveness.
 - Rely on multiple channels for communications and outreach to health professionals from many disciplines to assist in recruitment of study populations.
 - Develop media outreach strategies with spokespersons who can serve as role models and emphasize ethnically targeted messages, when appropriate.
 - Use informal communication networks to promote enrollment and compliance with clinical protocols.
 - In all outreach efforts, adapt the language of science to the needs of patient groups. Make efforts to accommodate alternative ways of learning, including the use of low-literacy materials.
 - Conduct community consultation and proper staff training to accommodate the special needs of study populations of clinical studies.
 - Provide access to health research programs and facilities for women to the fullest extent possible, including transportation services.
 - In order to enhance participant retention, develop flexible schedules at study sites, provide alternative service delivery such as the use of at-home examinations, complete medical insurance coverage for study participation, and day-care services.
 - Establish and use role models and advisory boards from the community to help direct programs. Use community confidants to help engender a sense of trust and guarantee of confidentiality.
 - Capitalize on the potential success of community partnerships in meeting recruitment and retention goals by initiating the partnerships early in the planning process.
 - Identify representatives of broad-based groups, including spiritual, religious, and business leaders, to participate in partnerships with the research institution.
 - Use research team members with similar racial, ethnic, and language backgrounds as the potential study participants. Whenever possible, use women and minorities as principal investigators and educators to help inspire a greater sense of trust among female study participants.
 - Address sensitivity to gender, racial, and ethnic issues during research training. Stress the importance of developing mutual confidence between study participants and research staff. The importance of patient responsibility and decisionmaking skills should also be stressed.
 - Inform patients of findings of the protocol, to the fullest extent possible, by openly discussing the treatments and their implications.
 - Incorporate formal and informal sources of social support into the design and conduct of studies by developing cooperation between clinical study programs and communities.
 - Work with existing community structures such as church groups that can help make patients aware of clinical studies and help them cope with treatments once the study is initiated. Informal networks can be accessed through formal community structures.
 - Make the best use of all available community sources of data when studying poorly documented populations.
 - Include information on cultural, racial, and behavioral characteristics when defining special populations.
 - Make the fullest use of clinics, advisory boards, and other resources that serve a target special population; they have the ability to provide needed data about that group and can provide assistance in recruiting study participants.

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CURRENT EXPERIENCES IN WOMEN'S HEALTH RESEARCH

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Introduction

As the previous chapters have illustrated, investigators and women face many issues and barriers in their efforts to promote the full inclusion of women in clinical research. Current experiences in women's health research, several of which are described in this chapter, have not only demonstrated the challenges involved but also have provided valuable information about successful strategies for recruiting and retaining various segments of the female population, including minorities, older women, poor women, lesbians, and women with disabilities. These studies have shown that, although many successful recruitment and retention principles apply to women and men, there are special considerations that apply to women in general and to certain populations of women in particular. Thus, experience suggests that recruitment techniques must be tailored not only to the study's design, but also to the targeted study population.

Recruitment Strategies

MULTIPLE MASS MEDIA OUTREACH

The collective experience gained through current studies demonstrates that the recruitment and retention of different types of women into clinical studies is feasible when a wide variety of strategies is used. The Postmenopausal Estrogen/Progestin (PEPI)¹ study, for example, demonstrated that large numbers of women can be recruited for a clinical trial when a direct appeal is made by multiple strategies, when the prevalence of the target condition is high, and when eligibility criteria are broad.

PEPI is a multicenter, double-masked, randomized, placebo-controlled clinical study that compares the effects of unopposed estrogen and three estrogen-progestin combinations on multiple cardiovascular risk factors. Participants must complete 10 clinic visits over 3 years and undergo multiple procedures, including venipuncture, bone-density measurements, electrocardiograms, mammograms, endometrial biopsies, and glucose-tolerance tests.

The PEPI study recruited 875 healthy, postmenopausal women over a 56-week period, exceeding the goal of 840. PEPI recruitment strategies included a wide variety of print and broadcast media communications and community-based approaches that appealed directly to the target

group. These strategies included publishing articles about the study and the clinics in local newspapers, advertising the study through mass mailings and radio and television news media, and televising interviews with clinic staff and physicians. Five of the seven clinics involved in the study found that local newspaper articles about the study, mass mailings, or television interviews were most efficacious. While a national publicity campaign produced a low direct yield, it did generate local media interest in the study. The recruitment organization included a coordinator for each clinic and central monitoring that provided regular and frequent feedback about each clinic's progress. Retention through the screening process was also successful. Careful telephone screening of approximately 8,400 women resulted in 1 woman being randomly assigned to a study group for every 10 calls made; for every 2 women among the 1,466 who attended the initial screening visit 1 was randomly assigned.

SINGLE MASS MEDIA OUTREACH: MASS MAILINGS

The Women's Health Trial (WHT): Feasibility Study in Minority Populations² successfully used mass mailings to recruit minority women and women from diverse socioeconomic strata into a broader nutrition study called the "Women's Health Trial."

The WHT is a cooperative effort among the NIH's NCI and NHLBI, the Fred Hutchinson Cancer Research Center in Seattle, and several clinical centers, including the University of Alabama-Birmingham, Emory University in Atlanta, and the University of Miami, Florida. The primary purpose of the WHT was to determine the feasibility of recruiting healthy, postmenopausal women, especially minorities, into a year-long nutrition study. The selection of the clinical centers was based on whether the center's patients included a significant minority population from which participants could be recruited. Participants were recruited using a mass mailing strategy and were then randomly assigned into a high-fat or low-fat group.

Recruitment into the study was very successful, resulting in 934 participants. Recruitment of a significant percentage of minority women was achieved: Birmingham and Atlanta recruited 20 percent and 49 percent African-American participants, respectively, and 30 percent of recruits from Miami were Hispanic. Mass mailings resulted in a 7 to 10 percent response rate, which was significantly higher than expected.

ONE-ON-ONE HOME RECRUITMENT

The objective of the Cardiovascular Health Study (CHS)³ is to determine the risk factors for coronary heart disease and stroke and the consequent disability in men and women age 65 years or older. The study is

taking place in California, Maryland, North Carolina, and Pennsylvania and will continue until 1999.

Successful recruitment of women age 65 years or older was achieved by presenting information to them at their homes. In addition to personal recruitment, the following factors were found to enhance the enrollment of these women in this study:

- Study legitimacy (and perceived legitimacy).
- Community physician approval.
- Interviewers who were middle-age or older.
- Interviewers who were gracious and assertive.
- Individualized attention to participants.
- Tokens of appreciation.
- Flexibility.

In all, 2,942 women have been recruited into the study, compared with an expected enrollment of 3,000. Most are married, high school graduates, and have an income in excess of \$16,000. Retention in the study has been excellent, with approximately 94 percent of women remaining in the study after 4 years.

Another example of this successful recruitment strategy is the Strong Heart Study,⁴ a study of cardiovascular disease in Native Americans that was begun in 1988 and is sponsored by the NHLBI in cooperation with Medlantic Research Institute, University of Oklahoma, and Aberdeen Indian Health Service. Investigators in this study faced the challenge of a target study population that was widely scattered over large rural areas⁵ in Arizona, Oklahoma, North Dakota, and South Dakota. A frequent lack of telephones or modern roads further complicated recruitment. To overcome these barriers, investigators relied upon individuals who were hired from the study population to make personal visits to many tribal communities; these individuals also assisted in conducting examinations during the trial, which successfully studied a total of 4,559 patients over a 3-year span.

HOME STUDY PARTICIPATION

Currently in its baseline phase, the objective of the Women's Health and Aging Study (WHAS)³ is to determine the major diseases and conditions responsible for physical disabilities and changes in disabilities over time in moderately-to-severely disabled women age 65 years or older. Potential participants had to experience difficulty in two or more of the following areas:

- Mobility tasks.
- Upper extremity tasks.
- Instrumental activities of daily living.
- Self-care tasks.

In order to successfully recruit disabled women, investigators designed the study so that examinations and interviews were provided in the convenience and privacy of the participants' homes. In addition to home study participation, the following factors were found to enhance enrollment of disabled women in the WHAS:

- Outreach to physicians and family members.
- Appeal to generativity (participants will be helping their daughters, granddaughters, and sisters).
- Interventions by interviewers (interviewers provide support on issues facing participants such as distress and depression).

Fifty disabled women have been enrolled in the study to date. Sixty-six percent of the participants are white, have at least an eighth-grade education but have not received a high school diploma, and most rate their health as fair or poor. There is a higher percentage of participants in this study with chronic conditions as compared with the Cardiovascular Health Study participants.

Retention Strategies

Most of the studies cited in the chapter have reported that retention is not as severe a problem as recruitment. However, many of the logistical and financial barriers described in previous chapters also contribute to low rates of retention. The continued provision of assistance in child care, transportation, insurance coverage, and other areas is essential if participants are to complete the study. In addition, the development of close, personal relationships between staff and study participants also seems to play an important role in retention.⁵ Minorities and people of low socioeconomic strata often have many problems in addition to the condition being studied, for example, homelessness, unemployment, marital problems, or financial problems. Differences in ethnic values and cultural attributes can also have an effect on retention. An attitude of caring and assistance on the part of investigators and staff may keep participants returning to the facility not only to participate in the study but also for the personal and social contacts.

Sensitivity on the part of study staff toward the unique needs and attitudes of all women and a willingness to accommodate those needs appears to be a hallmark of effective recruitment and retention. It is not enough to recruit women into clinical studies; it is critical that researchers help women be *successful* study participants. In the NHLBI's Pawtucket Heart Health Program (PHHP) study, for example, even though women made more attempts than men to change their risk factor behaviors, the men were more successful. The PHHP researchers

discovered that by accommodating women's needs female participants could be successful. For example, female participants in the PHHP who needed to lose more than 50 pounds told investigators that they felt uncomfortable meeting with thinner women in weight loss groups. At their request, a weight loss group was established for them and has been extremely popular and successful.

Other Examples of Successful Clinical Studies Involving Women

Malama Na Wahine Hapai: Caring for Pregnant Women.⁶ In this Hawaiian study, begun in 1990 and conducted by Emory University in collaboration with the State of Hawaii Department of Health, researchers use radio and cable TV public service announcements and special sections in a local newspaper, among other resources, to recruit for their clinical study. In addition, study investigators establish relationships with leaders of prominent businesses and community service organizations to promote study enrollment; these partnerships have helped to ensure that study protocols and recruitment methods are culturally sensitive. Using such partnerships, person-to-person communications, and the media, the study continues to maintain exceptionally successful recruitment and retention.

Another distinguishing attribute of this study is that researchers actively integrate and honor study participants' choices involving cultural and ethnic healing. By consulting indigenous scholars and inviting them to serve as project counselors and consultants, researchers are able to work in harmony with the participants by respecting their long-standing cultural beliefs and have successfully garnered the trust of the study population.

Heart, Body and Soul, Inc.⁷ This east Baltimore, Maryland, community-based study has faced a number of significant issues in recruitment, retention, and study design. The community is one in which 75 percent of residents' income is allocated to housing, and 14 percent of all eligible adults are unemployed. For many of these people, attention to health issues, including enrollments in clinical studies, is secondary to basic human needs, for example, adequate housing, nutrition, and protection from violence. Substance abuse and the effects of crime have also had a devastating influence on individuals, blocking their ability to even consider clinical trial participation.

In addition to these issues, the study designers had to overcome a history of strained relations between The Johns Hopkins Medical Institutions, which was the host medical institution, and the surrounding community. Among the obstacles was a sense of mistrust based on community

experiences in the institution's emergency room and other treatment facilities. One of the sponsors of Heart, Body, and Soul, the Clergy United for Renewal in East Baltimore (CURE), was instrumental in building bridges between study sponsors and the community where 65 percent of the population attends church. With leadership roles and responsibilities equally vested in the community and the sponsor, strategies were developed and implemented that maximized local acceptance of the program.

Today, Heart, Body, and Soul operates three centers with more than 300 trained volunteers and 32 staff members. Neighborhood health workers provide prevention, health education, monitoring, referral, followup, and support services. Regular screening services are offered and rapid-access clinics are available for immediate referral into specialized treatment centers.

Summary

A number of clinical research projects have demonstrated that improved recruitment and retention can be achieved. Many of the recommendations suggested in earlier chapters—increased sensitivity to cultural and ethnic attributes of individuals and communities, greater attention to the financial and logistical barriers faced by potential participants, increased attention to inclusion issues during study design and staffing phases—were put to successful use in the studies highlighted in this report.

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CONCLUSIONS AND RECOMMENDATIONS

Lewis H. Kuller, M.D., Dr.P.H.

It is clear from the information contained in this document that if women, especially minority or low-income or rural women, are to be successfully recruited into clinical trials, new approaches to the conduct of clinical research must be substituted for the traditional practices that have created the barriers currently associated with clinical studies. These new approaches may constitute more than a procedural change for clinical research institutions. Along with the medical establishment as a whole, these institutions must undergo true, fundamental changes in their prevailing culture.

Clinical research can no longer be carried out in isolation from the broader needs and interests of the communities in which it is conducted. For women in particular, partnerships must evolve that promote mutual trust and respect. Study protocols must appeal to and support women and be implemented in full consideration of the cultural traditions and obstacles faced by women of diverse racial and ethnic backgrounds and socioeconomic strata.

Current experiences in health research demonstrate that recruitment of various groups of women can be successful if the study designs are properly tailored and if appropriate recruitment strategies are used. The research project and benefits of participation need to be explained clearly and in a culturally appropriate manner to all potential participants. Mass media strategies can be effective; more personal approaches, for example, home visits and recruitment through clinics and personal physicians, can also be very effective. Retention of participants in studies requires equally diligent attention to the needs of the participants.

At the same time, regardless of the design features and implementation methods that are chosen for a study, it is critical that investigators uphold high standards of scientific integrity so that all data obtained are valid and applicable to a larger population. Recognizing issues related to women and minorities in clinical studies and incorporating the recommendations for addressing those issues into study design and implementation will help to provide clinical data that may fill the research gaps on women's health issues.

Efforts to fully include women, minorities, and those from diverse socioeconomic strata in clinical research have been ongoing for some years and will continue to flourish. Future reviews of ongoing research efforts will provide additional "lessons learned" and will guide researchers toward even more effective means of recruiting and retaining study participants.

Summary List of Recommendations

- Determine gender representation in clinical studies based on the research question to be addressed and the base rates of the illness by sex or by rates of morbidity or mortality for the illness by sex.
- Incorporate extra visits and flexible scheduling needed by women into the study design.
- Increase support for studies into the issue of hormonal and other biologically driven, gender-based differences to determine the impact of these differences on drug and treatment responses.
- Conduct research on the social and psychological barriers to women's participation in clinical studies.
- Include the participant's own health care provider in the study, if possible, so that the bonding achieved in this relationship can be carried over to the research setting.
- Encourage meta-analyses and/or pooled analyses on existing data sets of women and minorities that are too small to be analyzed individually in an economical fashion.
- Ensure that all aspects of a study, from its planning through its execution, are sensitive to the cultural, linguistic, socioeconomic, and logistical characteristics of the populations studied. For example, this should include involving women and minorities in designing the research, in preparing study materials, and in interacting with participants in a culturally and linguistically sensitive manner.
- Resolve the issue of lack of insurance coverage for treatment of incidental medical conditions and research-associated side effects to promote the inclusion of women in clinical trials.
- Analyze the goals and purposes of clinical studies to identify issues of particular relevance to women.
- Include women in the strategic planning process and use them in visible, key positions in the study, whenever possible.
- Plan and establish infrastructure to support both multicenter and community-based disease treatment and prevention studies, and use current exploratory models to develop estimates of the dimensions, performance, and utility of proposed future networks.
- Make efforts to gather, analyze, and evaluate information concerning the process of establishing and maintaining research partnerships.
- Expand the role of IRB's to encompass research funded by non-Federal agencies and the ongoing process of research.
- Involve IRB's in the early design phases of research to ensure that there is an equitable blend of study subjects.
- Ensure that all participants' questions about the study and possible side effects of treatment are answered fully and comprehensibly; avoid even subtle intimidation of study participants.
- Develop cost-effective recruitment approaches that combine strategies aimed at involving women as a group and also women of a particular race, socioeconomic status, age, risk profile, or geographic location.
- Encourage partnerships and networks, which are excellent methods for recruitment of diverse female populations, and disseminate information about successful recruitment strategies such as screening, counseling, and referral events (SCOREs), which were developed for the Pawtucket Heart Health Program.
- Nurture positive attitudes and beliefs by establishing and maintaining, whenever possible, one-on-one relationships that foster mutual trust and respect between research staff and study participants.
- Include women in clinical trial staffs, particularly women of the same ethnic or racial origins as those in the study population to the greatest extent possible.
- Promote joint decisionmaking and informed consent to the maximum extent possible so that participants are empowered to become active participants in their own treatment.
- Encourage interactions and facilitate the establishment of educational and support networks between former and current study participants to help support positive attitudes.
- Make participation in clinical studies possible for women, regardless of their ability to pay. The use of financial incentives, without creating an undue influence, is an appropriate recruitment tool.
- Adapt program designs that overcome the barriers to women's participation, particularly minority women and women from low socioeconomic strata. Examples of such actions include maintaining extended and flexible study clinic hours, providing transportation and child care, and developing study materials that are culturally and linguistically appropriate.

-
- Plan carefully, select communications channels judiciously, and pretest thoroughly before launching recruitment efforts. Followup is also essential and should include solicitation of feedback and evaluation of program effectiveness.
 - Rely on multiple channels for communications and outreach to health professionals from many disciplines to assist in recruitment of study populations.
 - Develop media outreach strategies with spokespersons who can serve as role models and emphasize ethnically targeted messages, when appropriate.
 - Use informal communication networks to promote enrollment and compliance with clinical protocols.
 - In all outreach efforts, adapt the language of science to the needs of patient groups. Make efforts to accommodate alternative ways of learning, including the use of low-literacy materials.
 - Conduct community consultation and proper staff training so as to accommodate the special needs of study populations when designing clinical studies.
 - Provide access to health research programs and facilities for women to the fullest extent possible, including transportation services.
 - In order to enhance participant retention, develop flexible schedules at study sites, provide alternative service delivery such as the use of at-home examinations, complete medical insurance coverage for study participation, and day-care services.
 - Establish and use role models and advisory boards from the community to help direct programs. Use community confidants to help engender a sense of trust and guarantee of confidentiality.
 - Capitalize on the potential success of community partnerships in meeting recruitment and retention goals by initiating the partnerships early in the planning process.
 - Identify representatives of broad-based groups, including spiritual, religious, and business leaders, to participate in partnerships with the research institution.
 - Use research team members with similar racial, ethnic, and language backgrounds as the potential study participants. Whenever possible, use women and minorities as principal investigators and educators to help inspire a greater sense of trust among female study participants.
 - Address sensitivity to gender, racial, and ethnic issues during research training. Stress the importance of developing mutual confidence between study participants and research staff. The importance of patient responsibility and patient decision-making skills should also be stressed.
 - Inform patients of findings of the protocol, to the fullest extent possible, by openly discussing the treatment and its implications.
 - Incorporate formal and informal sources of social support into the design and conduct of studies by developing cooperation between clinical study programs and communities.
 - Work with existing community structures such as church groups that can help make patients aware of clinical studies and help them cope with treatments once the study is initiated. Informal networks can be accessed through formal community structures.
 - Make the best use of all available community sources of data when studying poorly documented populations.
 - Include information on cultural, racial, and behavioral characteristics when defining special populations.
 - Make the fullest use of clinics, advisory boards, and other resources that serve a target special population; they have the ability to provide needed data about that group and can provide assistance in recruiting study participants.

THE OFFICE OF RESEARCH
ON WOMEN'S HEALTH
NATIONAL INSTITUTES OF HEALTH

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SCIENTIFIC MEETING:
RECRUITMENT
AND RETENTION
OF WOMEN IN
CLINICAL STUDIES

TASK FORCE
ROSTER

HOLIDAY INN BETHESDA
BETHESDA, MARYLAND
JULY 12-13, 1993

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THE OFFICE OF RESEARCH
ON WOMEN'S HEALTH

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEARING
ON THE
RECRUITMENT
AND RETENTION
OF WOMEN IN
CLINICAL STUDIES

SUMMARY

BETHESDA HOLIDAY INN
BETHESDA, MARYLAND
MARCH 29-30, 1993

Appendix II—Contents

FOREWORD	43
INTRODUCTION	45
OPENING REMARKS	46
<i>Vivian W. Pinn, M.D., Director, Office of Research on Women’s Health National Institutes of Health</i>	
REMARKS	47
<i>Antonia C. Novello, M.D., M.P.H., Surgeon General, Public Health Service U.S. Department of Health and Human Services</i>	
REMARKS	48
<i>Dianne Murphy, M.D., Assistant Director for Medical Affairs, Division of Anti-Viral Drug Products Center for Drug Evaluation and Research, Food and Drug Administration U.S. Department of Health and Human Services</i>	
SUMMARY OF ISSUES AND RECOMMENDATIONS	50
ISSUES AND RECOMMENDATIONS	52
<i>ISSUE 1: Regulatory and Legal Issues</i>	
<i>ISSUE 2: Cost and Insurance Issues</i>	
<i>ISSUE 3: Study Design and Research Staffing Issues</i>	
<i>ISSUE 4: Perspectives of Potential Study Subjects</i>	
<i>ISSUE 5: Special Concerns for Recruiting Low-Income and Minority Women</i>	
PARTICIPANTS	59

FOREWORD

The Office of Research on Women's Health (ORWH) was established within the Office of the Director of the National Institutes of Health (NIH) in September 1990. It was charged with the critical objectives of giving a central NIH focus to women's health issues and of establishing a science base that will yield reliable diagnoses as well as effective treatment and prevention strategies for women.

The Office of Research on Women's Health recognizes the enormous actual and potential contributions of women to the advancement of science, not only as full members of the scientific and research communities but also as participants in the clinical research process. We applaud recent efforts to increase the inclusion of women in clinical research studies but are concerned about the continuing underrepresentation of women in these trials.

It has become increasingly clear that we cannot continue to assume that risk factors for diseases are the same for women and men, nor can we assume that treatment and prevention interventions suitable for men are also applicable to women. The exclusion of women from important studies that examine lifestyle modifications, risk factor reductions, and intervention strategies for preventing morbidity and mortality from chronic diseases leaves a gap in knowledge regarding what behavioral changes are suitable and what interventions are appropriate in diagnosing, treating, and preventing diseases in women.

What can be done to bring more women into clinical research? How can we eliminate gaps in scientific knowledge resulting from the previous exclusion of women from clinical studies? The Office of Research on Women's Health is looking to the scientific and educational communities and to women's advocates to provide us with assistance in convincing the research establishment of the benefits of having more women participate in clinical research studies and formulating innovative strategies for overcoming the barriers women experience when participating in studies.

We appreciate the participation of all who have contributed to this process.

Vivian W. Pinn, M.D.
Director
Office of Research on Women's Health
National Institutes of Health

INTRODUCTION

In recent years, the NIH, scientists, health care professionals, congressional representatives, women's advocacy groups, and the public have become increasingly aware of the underrepresentation of women in clinical research. This has led to a greater interest in the inclusion of women in biobehavioral studies. Analysis of issues have contributed to enhanced efforts to recruit and retain women of diverse racial and ethnic groups and socioeconomic strata into clinical research.

To define and delineate barriers to the participation of women in clinical studies, the ORWH held a public hearing on March 29-30, 1993. In response to a *Federal Register* notice dated March 4, 1993, 39 individuals and representatives of organizations presented oral and submitted written testimony. An additional 19 submitted only written testimony. The testimonies identified barriers and offered recommendations related to the participation of women in clinical research.

Recommendations presented at the public hearing are being incorporated into the planning for the "Recruitment and Retention of Women in Clinical Studies" scientific meeting to be held July 12-13, 1993, in Bethesda, Maryland. The objectives of the meeting are to:

- Generate innovative recommendations for action.
- Develop strategies for enhancing the participation of women in clinical research and for improving the design of research studies.
- Highlight successful strategies for recruiting and retaining women in clinical studies.

This document summarizes testimony presented at the public hearing. In some instances, statements are paraphrased or synthesized to encompass several similar recommendations. This summary groups issues and recommendations into five main categories. The document represents the viewpoints of those who provided testimony and does not necessarily represent the views of the ORWH or the NIH.

The emphasis in the summary on the concerns of women of diverse racial and ethnic groups and socioeconomic strata reflects the fact that one-third of the 58 testimony statements addressed issues of interest to this population. Presenters described social, economic, and health status factors of this population; the consequent need to include them in clinical studies; and the significant barriers affecting their participation in the studies.

A reference number is printed in parentheses () after those statements in which data are presented. This number refers to the number of the testimony as identified on pages 59 and 60. An attempt was made to state each recommendation only once, although it should be noted that many of them were offered by multiple presenters.

Opening Remarks

PUBLIC HEARING RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES 29 MARCH 1993

Vivian W. Pinn, M.D., Director, Office of Research on Women's Health, National Institutes of Health

The Office of Research on Women's Health (ORWH) was founded in September 1990 by Dr. William Raub, then acting director of the NIH. The impetus for the establishment of this office, within the Office of the Director of NIH, was a recognition resulting from a General Accounting Office (GAO) Report in June 1990 that the NIH had not fully implemented its 1986 policy encouraging the inclusion of women in clinical research.

Attention to the inclusion of women in clinical research has escalated into a far-reaching priority not only for the NIH but also for members of Congress, the wider scientific community, and women's advocacy groups.

The 1985 Report of the Public Health Service Task Force on Women's Health Issues stated: "Biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups." Yet, only recently has the full implementation of this directive become a priority of the medical and scientific communities. This directive is central to the mandate for the Office of Research on Women's Health at NIH.

The ORWH has as its mandate to give NIH a central focus on women's health issues and to establish a science base that will permit reliable diagnoses and effective treatment and prevention strategies for women.

The major objectives of our office are:

- To develop an integrated strategy for increased research into diseases, disorders, and conditions that are unique to, more prevalent among, or more serious in women, or for which there are different risk factors of interventions for women than for men.
- To ensure that women are appropriately represented in biomedical and biobehavioral research studies, especially clinical trials, that are supported by NIH.
- Direct initiatives to increase the number of women who are participants in biomedical research careers.

The second objective, ensuring participation of women in study populations, especially clinical trials, is one of the highest initial priorities of our office. Women cannot expect to gain equitably from new advances in therapy and interventions if they are not included in the clinical trials that assess safety and efficacy.

The NIH has implemented a strengthened and revitalized policy on the inclusion of women and minorities in study populations.

The policy clearly states that adequate numbers of women shall be included in clinical studies proportional to prevalence among women of the condition under study. NIH funding components will not fund or award grants or contracts until the applicant provides sufficient information on the study population to ensure compliance with the NIH policy on inclusion of women and minorities in study populations.

We have further instituted a tracking system in order to monitor compliance with this policy, and the results are beginning to be analyzed for the first year of the system's implementation.

Why have women often been excluded from research? Was their exclusion an act of discrimination or of protection? Some of the reasons stated for the exclusion have been:

- Women's cyclical hormonal changes may confound research results.
- Study populations would be less homogeneous.
- Study costs would be higher if gender-specific hypotheses or subgroup analyses are anticipated.
- Recruitment of women into studies is more difficult.
- Legal and ethical issues surround potential exposure to a fetus.

However, because many treatments and modalities will be used in pregnant women, women of childbearing age, elderly women, women of diverse racial or ethnic origin, and women of varied socioeconomic circumstances, there is a need to know and understand potential effects and/or effectiveness of diagnostic efforts, treatment, and prevention in these populations and not just to infer their application to women from studies in men.

Through a contract, NIH is working with the Institute of Medicine (IOM) to address the legal and ethical implications of including more women in more clinical studies. The NIH and the IOM are developing recommendations to overcome some of the barriers investigators and administrators face in facilitating the applications of treatment for women from studies in men through the system while still keeping women's health, and that of any potential conceptus, at the forefront of their consideration.

If we are to fully address gaps in knowledge about women's health, we must succeed in our efforts to recruit and retain women in clinical studies. To assist us in this endeavor, we have formed a Planning Task Force on the Recruitment and Retention of Women in Clinical Studies. The task force has as its goals to:

- Assess the experiences of clinical trial researchers, practitioners, and women participants in the recruitment, retention, adherence, and compliance of women in clinical research.
- Identify issues and barriers unique to the recruitment and retention of women of all races and socioeconomic strata involved in different types of studies, with a particular emphasis on clinical trials.
- Review models and approaches that enhance the participation of women in clinical research.
- Develop a summary report with recommendations for improving access, participation, and retention of women from all racial and ethnic groups and socioeconomic strata in clinical research.

This public hearing has been convened to provide guidance and assistance to address the inclusion of women in clinical research through proven and improved methods for the recruitment and retention of women in biomedical and biobehavioral research and to eliminate barriers to their inclusion.

Recommendations from this planning task force will be submitted to the director of the National Institutes of Health and made available to the scientific and lay communities.

We appreciate your participation in this process, and look forward to your recommendations and expertise.

**PUBLIC HEARING
RECRUITMENT AND RETENTION
OF WOMEN IN CLINICAL STUDIES
29 MARCH 1993**

Antonia C. Novello, M.D., M.P.H., Surgeon General, Public Health Service, U.S. Department of Health and Human Services

We have made progress in the past few year, thanks to all the women in biomedical careers and the activists who have insisted on equality, at least some equality, for women in biomedical research. But colleagues, we haven't done *enough*.

The Women's Health Initiative is a clinical trial whose time has come. But other trials, equally important, aren't even on the "drawing boards," and they are needed as well.

This country is far more diverse than we can imagine and needs far more prevention and health care than what we have now. Let's not forget that this is a country of 250 million people, more than half of them women. More than 15 percent of our population is African-American, more than 9 percent Hispanic, 3 percent Asian Pacific Islander, 1 percent Native American, and almost 1 in 5 of our citizens is under 12 years of age; and more than 1 in 10 is over age 65. We have to shape our research and our thinking to meet these demographic realities; otherwise, we will be practicing and planning in a vacuum.

I think we must guard against refighting old battles. We have won the battle that women's diseases must be studied. We've whipped all the dead horses about clinical trials, about aging, aspirin, beta carotene and the like—trials well known to have excluded women. We have embarrassed some scientists and some institutions and raised consciousness of the neglect of women's health issues. Now we must polish our act and come up with some new tactics and strategies for action.

We need to be in total command of the relevant facts. And we must not be bought off by a few new clinical trials or old ones being repackaged with new "women's this or that" names. We must really "get our act together," and, for that, this hearing is a welcome and well-planned first step.

We not only need to look at the diseases that ravage and shorten the lives of women, but we must find how to get women into clinical trials and look at the subgroups most severely affected by diseases as well. We need to look at HIV, AIDS, heart attacks, stroke, cancer—especially breast, cervical, and lung cancer—osteoporosis and Alzheimer's disease. We need to monitor tuberculosis, and we need to look at diseases such as diabetes. And we need to do this soon.

Equally, we mustn't forget alcoholism, drug addiction, and depression as well as other mental illnesses. We are going to need the maximum sophistication to see that more women are added to ongoing as well as new trials. We must also seriously reconsider whether simply adding women to research protocols should be our number one task as we move ahead under our mandate to equalize women in research. This is especially important in cases where the answers given by current research on men are useful to women. In the search for parity and quality, our credibility must always remain a top priority.

I won't rehash the old clinical trials mentality, which excluded women from studies. Ours is a new day. We are learning in our clinical trials to address the complexities of women, their shifting hormonal patterns, and their needs. We have accepted that if medications or treatments are to be used on women, they should be tested on women.

Look at the numbers: approximately 249,000 women will die of cancer in 1993. About 365,000 women will die of heart attacks and about 100,000 of stroke this year. About 6.2 million women will suffer serious depression in any given month.

But as important as all of those items are, we also know that we need to help women who face multiple daily life issues today to become part of the research mainstream. No less important, women are going to need the best research in diagnosis, treatment, and rehabilitation, and they will need to be part of the planning system as well.

Research must address conditions such as low educational status, low expectations and self-esteem, substandard living conditions, unemployment, risk-promoting lifestyles, environmental and occupational toxic exposures, and diminished access to prevention and screening. They all must be part of the research protocol.

We know that poverty or affluence, access to medical care or lack of it, access to information or lack of appropriate information makes a life and death difference for women in some cases.

Let's talk a minute about another issue and see how our past endeavors sometimes come full cycle. Between 1948 and 1971, many pregnant women were given diethylstilbestrol (DES) in an attempt to prevent miscarriages and preterm births, exposing an estimated 9 million children in utero to DES. Now epidemiologic studies are being conducted by NCI to determine the aftermath of the DES exposure on the mothers and the children and to assess the occurrence of cancer, genitourinary abnormalities, and other diseases.

Are there other drugs or therapies being prescribed for women, still unstudied and affecting women and their children yet to be born? Are we still going to continue to study women as mothers and not *women as women*? Let's make it a point to answer these questions.

At the same time, in our quest for biotechnology, let us not forget for whom studies are intended. We need to be utterly practical and realistic and never think that "women" comprise a unified group. Social issues affect women in devastating ways. The woman's role in the family, the pressures on her to maintain discretion and confidentiality, the role she plays to safeguard culture, her responsibilities for her children, her financial and emotional dependence on a man or on herself—these issues all enter into her ability to consider enrollment in clinical trials and to use health care services at all.

Although there is a tremendous need for educating women, there is also a tremendous need for educating health care professionals regarding women's concerns as well. The examples that come to mind are gynecologic infections such as candidiasis and pelvic inflammatory disease and human papillomavirus, genital ulcers, cervical dysplasias, and genital warts.

We all know that regarding HIV, women have been so underdiagnosed that many first learned of their own HIV infection when their children were diagnosed.

Let me talk to you now about clinical trials and AIDS. As Surgeon General, I have seen the devastation of AIDS. Today, most women with AIDS are either African-American (53 percent) or Latino (21 percent). Between 30,000 to

40,000 African-American or Latino children will lose both parents to AIDS between 1995 and the year 2000. About 71 percent of the women diagnosed with AIDS have been sexual partners of intravenous drug users or have injected drugs themselves.

In the presence of such data, why is it that so many people with AIDS have either been excluded or not included in the services that do exist?

Allow me to tell you why. Women have told me that:

- Women are discriminated against because of their childbearing potential.
- Women mistrust the system—after all, clinical trials have been designed by men for men, and those men have never "walked in the shoes" of a woman.

Women and their health care providers have told me that:

- Clinics are not open at the times women can go. They are not found in the places women can reach. They are on floors too high for the women who are sick to climb stairs when there are no elevators. And the clinics are tended by people they can't understand.
- Women are requested to pay too many visits, without any consideration for the transportation costs involved and the respite and child care needed. Food is not available in the clinics. Who will feed their children?
- There is no "one-stop shopping"—care for the woman, her children, and husband all in one place. Family unity is disregarded in the presence of HIV infection.
- Too much blood is drawn without apparent coordination among laboratories. Are people guinea pigs?
- There are no facilities for their children at these clinics—no place for them to play, to be cared for, or to feel welcome.
- Too much medication is being prescribed without explanation or understanding of what 28 pills a day can do to a woman's life, to a woman's time.
- There is a fear that the side effects of hunger are being confused with the side effects caused by the medication itself.
- There is lack not only of language sensitivity but of cultural sensitivity as well.
- No explanation is given about why participation in clinical trials is important for the entire family and not only as a cure for the mother. Families need to be considered as a whole.
- They fear upsetting their mates, they fear abandonment by the community.

- They fear being thrown out of a clinical trial if side effects become evident. Where do they go next? Will they be given AZT again? Who will place them back on routine care?
- There is a lack of adequate communication about contraceptives. What might be adequate contraception in some communities may be inadequate contraception for some others, especially where “the rhythm method” is employed but no one acknowledges or asks about it. Any discussion of this issue must be linguistically and culturally sensitive. If contraception is needed as part of a clinical trial, who will provide for this, and who will pay?
- Women, in some cultures, must have permission from their husbands in order to participate in a clinical trial. In the absence of this approval, they are unable to comply.
- There are no caseworkers outside of the clinic to explain why the trial is important in a sensitive, simple human way early on in the recruiting process.

In addition to addressing these problems, women have recommended that:

- Once information about clinical trials is available (and is linguistically and culturally appropriate), that information can then be widely disseminated.
- The care of children is linked to the care of women and linked to the care of the family. This reality must dictate the nature of the clinical trial and how it is administered.

Obviously, we need to know more about the biology of pregnant women with HIV and more about how the unborn child is affected by anti-retroviral drugs. It may make researchers feel more comfortable to exclude pregnant women from clinical trials, but, at the same time, it may rob women and children of important therapeutics. We need rapid progress on tests to determine if a child is infected and vaccines to protect the baby as well as the mother.

Currently, when information about HIV-related clinical trials is needed (both federally and non-federally funded), people are instructed to call the AIDS Clinical Trials Information Service. The HIV/AIDS clinical trials are usually listed by “adult” and “children.” Much searching is needed to find out how many trials enroll *women*. I think in all clinical trials, not just AIDS trials, we have to press the research community to make this information easily and readily available to all of us.

In addition, the concepts of safer sex have been predicated on partners with equality. I ask you, how many women can interrogate partners about their sexual histories or sexual patterns today and then make purely intellectual decisions about how, when, and if sex should occur? I think we’ve been highly unrealistic here, and unintentionally, we have been setting women up. The woman’s role in making such decisions depends on her value to her partner, their relationship, her value to her family, her value to her culture, and her value to her community, among other complex, mitigating factors.

We cannot continue to ask women to make decisions that rob them of their emotional and financial security. We still have a great deal of work to do in the area of safer sexual practices.

We need to consider all the socioeconomic, legal, and ethical issues that impinge on the health status of women. But we should recognize *what a woman can do versus what we want her to do*. Approaches should be more sensitive to her culture and to her realities, not only to our protocols.

We must not forget that poverty is associated with a high degree of insecurity in our society; it simply limits one’s options and ability to plan. Being poor may mean that you don’t have a telephone to call for information, or you don’t have the level of education to understand clinical procedures or the very concept of a clinical trial.

Let’s meet women in the middle. Let’s stop making them feel uncommunicative or uncaring. We must start giving poverty some respect and give women back their dignity.

Finally, I would like to correct a very pervasive idea. I often hear that poor people won’t comply with medical protocols or clinical trials. Maybe they *can’t* comply—not that they *won’t*, but they *can’t*. Maybe they *can’t* afford the bus fare, *don’t* have a baby sitter, *can’t* miss work, *can’t* pay for drugs or checkups. *Can’t*. Not that they *won’t*.

The time has come to end the fractionation of women. It is time to tear down the barriers and open wide the doors. We need an end to any self-limiting attitudes and an insistent appreciation of women’s worth.

As we move ahead to that point, we must monitor the process and participate in the outcome. But most importantly, we must remember that any successful effort to improve women’s health will have to include women as equal partners in the development of policies pertaining to them and to their families.

Thank you.

**PUBLIC HEARING
RECRUITMENT AND RETENTION
OF WOMEN IN CLINICAL STUDIES
29 MARCH 1993**

Dianne Murphy, M.D., Assistant Director for Medical Affairs, Division of Anti-Viral Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services

I am Dr. Dianne Murphy, Assistant Director for Medical Affairs in the Division of Anti-Viral Drug Products, at the Center for Drug Evaluation and Research, Food and Drug Administration (FDA).

I am here today representing Dr. David Kessler, Commissioner of Food and Drugs; Dr. Ruth Merkatz, the Commissioner's Special Assistant for Women's Health; and the FDA Working Group on Women in Clinical Trials.

Like our colleagues at NIH, we at the FDA have been concerned about the issues surrounding the inclusion of women in clinical trials.

During the past several years, a number of events have helped to focus attention on women's health issues. To name just a few, a Public Health Service (PHS) task force established in 1985 concluded that women were disadvantaged both in terms of health care and access to biomedical and behavioral research. The PHS task force recommended that steps be taken to address the overall health needs of women—from bench to bedside. In the 1980's and early 1990's, the Congressional Women's Caucus was formed on the Hill, the Women's Health Equity Act was introduced in the U.S. Congress, an increasing focus on women's health occurred at NIH, and advocacy organizations made their influence felt in promoting a national women's health research agenda.

Over the past decade at FDA, there have been many internal discussions and analyses focused on the appropriate inclusion of women in clinical trials. In addition, we have sought guidance and input externally by cosponsoring or participating in a number of scientific conferences to examine relevant issues: the Institute of Medicine's (IOM) March 1991 planning meeting on the inclusion of women in clinical trials, the Institute of Medicine's Drug Forum on Women and Drug Development in June 1992, and the Food and Drug Law Institute's Workshop on Women in Clinical Trials of FDA-Regulated Products in October 1992.

Two important concepts have evolved from these scientific and ethical discussions: (1) those involved in drug development should include appropriate representation of women in their clinical studies, and the new drug applications that emerge from these clinical studies should

include analyses of potential gender differences; and (2) the FDA's 16-year general exclusion of women of "childbearing potential" from the earliest phases of clinical trials may no longer be appropriate.

Over the past year, the FDA has been working in an intensive, focused manner to develop new guidance designed to expand the number of women of childbearing potential in clinical trials of new drugs and biologics.

As you know, underlying the exclusion of women of childbearing potential was a desire to minimize unnecessary risk to a fetus in the event that a female subject became pregnant during exposure to an investigational agent. As we speak today in 1993, protecting a fetus from unanticipated exposure to potentially harmful drugs remains a principle of paramount importance in designing clinical trials. However, it is also important to consider the potential scientific benefits of including women of childbearing potential in earlier phases of clinical trials. Identifying important gender differences during the early phases of clinical studies may facilitate the appropriate design of critical later studies which, in turn, can further clinical understanding of the appropriate use of drugs in women. It should also be noted that we now have available a number of options to utilize in preventing and in quickly and accurately diagnosing pregnancy. These technical advances can be put to use in providing assurance that we are not unknowingly exposing fetuses to experimental therapies.

As Dr. Kessler has said, "In the past, medical research has focused on males and all too frequently women have been included as an afterthought. Eliminating these barriers is the right thing to do."

The FDA hopes the changes in the guidance concerning women during the conduct of clinical trials will contribute to our knowledge and understanding of the optimal use of therapeutic agents in women.

I would like to thank Dr. Vivian Pinn and Dr. Judith LaRosa for providing the FDA with an opportunity to participate in opening what, I am sure, will be an interesting and exciting couple of days of hearings. I look forward to the proceedings.

SUMMARY OF ISSUES AND RECOMMENDATIONS

Currently, women constitute approximately 51 percent of the U.S. population. On average, women also live 7.5 years longer than men. The elderly population—those over age 65—is growing rapidly, and, among those, the group over age 85 is growing the most rapidly. Women are the majority of this population, and they are more likely to spend their later years with multiple chronic health conditions.⁽⁵⁵⁾

Heart disease alone exacts an enormous toll in women, equivalent in scope to the toll in men.

- More than 244,000 women die of heart attacks each year and more than 90,000 die from stroke. Coronary heart disease and stroke rank first and third as causes of death for middle-age and older women. With each decade of life, the death rate from coronary heart disease increases threefold to fourfold.⁽⁵⁴⁾

Many other diseases also place a heavy burden of death and disability on women.

- Rheumatoid arthritis affects women three times as frequently as men.⁽⁵²⁾
- Systemic lupus erythematosus occurs nine times more often in women than in men.⁽⁵²⁾
- It is estimated that 2.6 million women live with breast cancer—1 million of whom are aware of their disease—1.6 million of whom are not yet diagnosed. It is estimated that in 1993 there will be 185,000 newly diagnosed cases and 46,000 deaths.⁽³³⁾
- Osteoporosis affects one-third to one-half of all women after menopause.⁽⁵²⁾
- At least 80 percent of the patients with scleroderma are women.⁽⁵²⁾
- Genital herpes or human papilloma virus infections affect 15 to 20 million women.⁽⁵⁶⁾

Perhaps, not surprisingly, women rely much more heavily on the medical system than do men. Approximately two-thirds of all visits to doctors and pharmacists are made by women,⁽⁴⁴⁾ and studies document greater health-seeking behavior in general by women as compared with men.⁽³³⁾

In the search for greater understanding of the etiology, diagnosis, treatment, and prevention of disease, numerous clinical research studies have been undertaken using human subjects. Yet, women have traditionally been underrepresented or excluded from many clinical studies. This exclusion has been made despite some clear evidence of gender-based differences in the progress of disease and the response to treatments.

- Many psychiatric disorders, including depression, schizophrenia, many personality disorders, and attention deficit hyperactive disorder, have different prevalence rates and courses in women and men.⁽¹⁾
- Women and men differ in their vulnerability to important medication side effects.⁽¹⁾
- Behavioral interventions designed to decrease high-risk activities (smoking or HIV infection) differ between women and men, for example, the interventions do not seem to work as well for women as for men.⁽¹⁾

- HIV infection may present differently in women and men; the challenges of living day-to-day with HIV also appear to be different for women and men.⁽⁴⁵⁾

Considerably more information is required on how women's different hormonal and physiological characteristics influence the progress of disease and the response to treatments. This makes application of research findings to the general population that have been derived solely from males questionable, at best.

Several reasons have been given for excluding women from studies,⁽²⁶⁾ including:

- Concerns about fetal safety preclude recruitment of women with reproductive potential.
- Hormonal changes associated with the menstrual cycle and other physiologic differences between women and men create major methodological problems in data collection and analysis.
- Women are difficult to recruit for studies and, once recruited, are more difficult to retain for the length of the study.

This has resulted in a situation in which gender-related factors are often used as reasons for excluding women from research populations. On the other hand, gender-related factors are ignored when health interventions derived from studies of men are generalized to the entire population.⁽⁴²⁾

In recent years, this situation has gradually begun to change in large measure because of:

- A revised NIH policy, issued in 1990, that requires applicants for clinical research grants to include women in study populations unless there is a "clear, compelling rationale" for their exclusion.
- A growing body of evidence showing that women have been systematically underrepresented in clinical research (e.g., the 1990 GAO report) and that they, in fact, do not refuse to participate in or drop out of studies in greater numbers than men.^(31,59)
- A growing appreciation by the scientific community of the need to recruit and retain women in clinical studies, particularly low-income and minority women.

Despite this changing environment, steps still need to be taken to achieve parity between women and men in clinical studies. During the public hearing, the issues involved in recruiting and retaining women fell into five major areas:

- Regulatory and legal issues.
- Cost and insurance issues.
- Study design and research staffing issues.

- Issues related to the perspectives of potential study subjects.
- Issues related to recruiting and retaining low-income and minority women.

Numerous recommendations were made in the areas listed below:

- Recommendations about changes to NIH policies to require inclusion of women in studies; changes in incentives for drug manufacturers were also suggested.
- Recommendations regarding changes in health insurance policies so that participation in research protocols is covered.
- Recommendations regarding the design of research protocols and materials, advancement of women and minorities in clinical research positions, and staffing of research studies with personnel who are bilingual and culturally sensitive.
- Recommendations regarding the needs, concerns, and characteristics of female study participants.

There was also a recognition that efforts to recruit and retain women in clinical research will result in greatly increased cost⁽⁴⁰⁾ because of the need for:

- Much larger sample sizes.
- Extended, more flexible research facility hours.
- Provision of child care, transportation, and appropriate incentives.
- Training and staffing of multiethnic research teams.
- Greater consultation and coordination with local communities in the design and implementation of clinical studies.

Issues and Recommendations

ISSUE 1 REGULATORY AND LEGAL ISSUES

Barriers⁽¹⁸⁾

Key players who decide what role women are to have in any given clinical study include:

- | | |
|-----------------------------|-------------------------|
| ■ Study sponsors | ■ Research institutions |
| ■ Federal regulators | ■ Women's advocates |
| ■ Potential female subjects | ■ Public officials |
| ■ Investigators | |

Some groups have used specific concerns as a basis for their policies regarding exclusion of premenopausal women in clinical research. Two of these concerns focus on:

- Possible harm to a fetus caused by the experimental treatment or drug.
- Possible harm to a female subject's reproductive potential.

In 1991, NIH issued strengthened guidelines on the "Inclusion of Minorities and Women in Study Populations." Although these guidelines strongly encourage applicants for research grants to include women, they list several permissible justifications for excluding them. Among these justifications is a provision stating that: ". . . the experimental procedures/treatments present unacceptable risks for women of child-bearing age." By not defining an "unacceptable risk," the guidelines allow a trial sponsor to cite any uncertainty about the treatment or drug's effect on fertility as meeting the exclusion justification.

Other barriers thought to be presented by drug manufacturers who, in some instances, determine that costs associated with including women in clinical trials outweigh any perceived benefits include:

- Liability for in utero injuries is a real possibility. The consent form a woman signs waiving the right to sue for any injuries suffered applies only to herself, not to any fetus conceived during the study.
- Manufacturers' legal liability can be reduced if fertile women are excluded from clinical trials, if the drugs are not actively marketed to them, and if warning labels are carried, even though the manufacturer knows that the drug will eventually be used by some pregnant women.

Recommendations

A number of people presenting testimony praised NIH for its recent steps in encouraging the recruitment of women in clinical studies and for its formation of the ORWH. They also made recommendations for changing the regulatory and legal climate to one that even more strongly favors the inclusion of fertile women:

- Emphasize early, extensive contraception counseling with women of childbearing potential who participate in studies.⁽³⁶⁾
- Encourage use of superior methods of contraception and use endocrine measures to detect very early pregnancy.⁽³⁶⁾
- Recruit study participants from the very large pool of premenopausal women for whom pregnancy is impossible or highly unlikely: celibate or homosexual women or those who have undergone tubal ligation or hysterectomy.⁽³⁶⁾

- Change the incentive structure for manufacturers by decreasing the threats posed by suits based on in utero injuries and by increasing the incentives for including fertile women.⁽¹⁸⁾
- Increase the number of women in leadership positions such as principal investigators of clinical trials, members of grant review committees, and members of conference planning and invitation committees.^(28,35)
- Continue to promote the advancement of women in biomedical careers.⁽⁵⁷⁾

The following recommendations were directed toward the Congress, the NIH, and the ORWH:

- Congress should pass proposed legislation that would codify NIH's policy on including women and minorities. This legislation would also require specific guidelines under which the inclusion of women is inappropriate.⁽¹⁸⁾
- NIH's current guidelines should be strengthened by a requirement that researchers detail strategies for recruiting and retaining women as part of the grant proposal.⁽¹⁸⁾
- NIH should award "bonus points" to proposals that suggest particularly effective or creative strategies for recruiting and retaining women.⁽³⁹⁾
- Increase efforts to attract and fund research proposals of qualified female researchers.⁽³⁵⁾

ISSUE 2 COST AND INSURANCE ISSUES

Barriers

Financial constraints pose a significant barrier to the participation of many women in clinical studies, particularly those brought about by the current system of health insurance.

- Virtually all third-party payers and health maintenance organizations (HMO's) include a clause in insurance contracts that excludes coverage for all costs associated with "experimental treatments."⁽²⁴⁾
- Medicare regulations also contain this exclusion.⁽²⁴⁾
- Depending on state guidelines, Medicaid regulations may also contain this exclusion.⁽²⁴⁾
- A recent Gallup survey indicated that, of those oncologists who refer patients to clinical trials, 29 percent said that lack of reimbursement posed a significant barrier to patients' participation.⁽²⁹⁾

If an individual participates in a clinical study, the usual procedure is for the sponsor to cover the costs of data collection and the drug or treatment being tested.

However, patients are responsible for hospital and laboratory fees and doctor services associated with the study.

The results of this policy indicate the following:⁽²⁴⁾

- Patients have limited access to important, sometimes life-saving treatments, even though they may cost less than standard treatments.
- Patients do not participate in trials unless they can afford the costs and are willing to pay them. This cuts out an enormous pool of lower income potential study subjects.
- Oncologists sometimes alter their choice of therapy in response to these reimbursement constraints.
- Patients are reluctant to appeal the decision when access to treatment is denied; many doctors do not know how to assist patients with an appeal.

Recommendations

A number of participants at the hearing were concerned about this issue and offered specific recommendations:

- Cover subjects' costs associated with participation in a clinical trial.^(24,33,39)
- Clinical studies should meet the following criteria if expenses are to be covered:⁽²⁹⁾
 - The treatment under study is therapeutic.
 - The treatment is a part of a trial approved by NIH, an NIH cooperative group, the FDA, Department of Veterans Affairs (VA), or a "qualified nongovernmental entity."
 - The proposed therapy is reviewed and approved by a qualified Institutional Review Board (IRB).
 - The facility is adequate and personnel are qualified.
 - There is no available noninvestigational therapy that is superior to the protocol treatment.
 - Available data suggest that the treatment will be as efficacious as noninvestigational therapy.
- The President's Health Care Reform Task Force should consider this issue and include some form of coverage in the minimum health care benefits package for all Americans.⁽²⁴⁾
- The NIH and professional medical associations should produce guidelines for clinicians on supporting their medical decisions to third-party payers.⁽²⁴⁾
- All NIH-sponsored clinical trials should require the designation of an individual to assist patients with insurance preapproval and appeal processes.⁽²⁴⁾

ISSUE 3
STUDY DESIGN AND RESEARCH STAFFING ISSUES

Barriers

Cyclic hormonal fluctuations and other physiologic gender-based differences create significant challenges in the design and execution of clinical studies. Measurements often need to be timed carefully during the subject's menstrual cycle, and, therefore, women may need to be seen for extra visits or may require frequent rescheduling because of unpredictable menstrual cycles. This has a number of repercussions for the design and budgeting of clinical studies, including:

- Increased financial and personnel costs.
- Need for larger sample sizes to account for the increased variability of data.
- A lack of comparability with data from previous studies that have included only male subjects.

Also at issue is the design and development of recruitment materials and documents related to the study protocols and design. Research protocols, consent forms, and other materials that are “incomprehensible, harsh, and culturally insensitive”,⁽¹²⁾ as they often are, effectively preclude the participation of many women, particularly minority women.

A further barrier to participation is posed by the staffing of clinical study teams because many women mistrust and feel intimidated by clinical research staff because of differences in gender, race, ethnicity, education, and socioeconomic background.

Recommendations

A number of recommendations were made at the public hearing on the subject of study design and staffing:

- Increase support for studies into the issue of hormonal and gender-based differences in order to determine the nature and extent of these differences on drug and treatment responses. The results of these studies could assist in the design of future studies.^(14,42)
- Conduct research on the social and psychological barriers to women's participation in clinical studies.⁽³⁴⁾
- Determine gender representation in clinical studies based on the base rates of the illness by sex or by rates of morbidity or mortality for the illness by sex.⁽³⁶⁾
- Encourage meta-analyses and/or pooled analyses on existing data sets of women and minorities that are too small to be analyzed individually in an economical fashion.⁽⁵³⁾
- Include women in the process of writing of proposals, research protocols, consent forms, and materials to be used with patients.⁽¹²⁾

- Include groups or individuals who represent the study population in planning the study in order to ensure a mutually acceptable research design.⁽⁹⁾
- Include, if possible, the subject's own doctor in the study so that the bonding achieved in the regular doctor-patient relationship can be carried over to the research setting as well.⁽⁶⁾
- Design clinical studies to accommodate the menstrual and hormonal cycles of subjects by including the need for extra visits and flexible scheduling in the protocol.⁽²⁶⁾
- Increase the numbers of clinical research staff—at both the junior and senior level—who are similar to the study population in demographics and ethnicity.⁽⁴³⁾
- Ensure that the staff members who work with study populations are bilingual and bicultural, if necessary.^(10,30)
- Encourage the full participation of junior research staff members, who are currently more likely to be the bilingual and bicultural staff members, in the planning and execution of clinical studies.⁽¹⁷⁾
- Ensure that staff is sensitive to the concerns, questions, and fears of female study subjects.^(30,32,35,38,43)

ISSUE 4
PERSPECTIVES OF POTENTIAL STUDY SUBJECTS

Barriers

A number of general barriers to the participation of women in clinical studies exist. These have to do primarily with the level of awareness and understanding that women have about the medical system and how it works. They can be characterized as follows:

- Women are often unaware of planned clinical trials or their eligibility to participate.^(33,34)
- Many women encounter a “gatekeeper” mentality from their physicians, in which they are not given information about a condition, therapy, or clinical study because it is deemed “too complex” or “unnecessary.”⁽³⁴⁾
- When women are told about clinical trials, many hesitate because they fear the unknown, are concerned about being a “guinea pig” in an “experimental” treatment, or feel that participation means that the physician is making a “last ditch effort” for the patient.⁽²⁴⁾

Frequently, the heart of the issue is a fundamental difference in approach to medical care and clinical research held by researchers and female subjects;⁽⁶⁾ the researchers' main interest is in the disease process

or drug under study, whereas the female subjects' concerns are with overall patient care and personal, sympathetic relationships with the personnel on the research team.

Recommendations

- Promote public education efforts about clinical trials that address patient fears and target appropriate literacy levels.⁽²⁴⁾
- Foster open discussion between care providers and patients so that the patient learns about the possibilities of participating in a trial and concerns, questions, and fears are allayed.⁽⁶⁾
- Maintain a full and open discussion of the study purpose and plan so as to find a middle ground between the researchers' and the subjects' objectives. Researchers should design a study in such a way that the subjects are truly cared for, not just studied.⁽⁶⁾
- Encourage closer relationships among local health care providers, universities, and research centers, particularly in minority communities, so that primary patient care and clinical research can be more closely integrated (i.e., the cancer care and research model) and information about clinical trials can be disseminated.⁽²⁹⁾

The following recommendations were directed to NIH and the ORWH:

- NIH should maintain a register of ongoing clinical trials that would be accessible to practitioners and the public.⁽³³⁾
- Research, including focus group studies, on barriers to participation and strategies for overcoming such barriers should be funded.^(34,59)
- Methods for tracking and monitoring enrollment and retention of women in clinical trials should be funded.⁽¹⁴⁾
- The ORWH should convene a task force to study the adaptation for medical schools of the American Medical Women's Association's *Advanced Curriculum on Women's Health* to assist physicians in providing a more sensitive and appropriate approach to women's unique health problems.⁽⁴⁶⁾

ISSUE 5 SPECIAL CONCERNS FOR RECRUITING LOW-INCOME AND MINORITY WOMEN

Barriers

Low-income and minority women constitute a key population of concern in the recruitment and retention of women in clinical research, not only because they have traditionally been excluded but also because of their high rates and high risk of major diseases such as heart

disease, cancer, HIV/AIDS, sexually transmitted diseases (STD's), tuberculosis (TB), and others.^(10,17)

- The majority of women with AIDS are African-American (53%) or Hispanic (21%).⁽¹⁴⁾
- Through perinatal transmission, AIDS is the leading cause of death among Hispanic children and the second leading cause for African-American children.⁽¹⁷⁾
- Rates of coronary heart disease and stroke are substantially higher in African-American women than in white women.⁽⁵⁴⁾

This key population includes diverse groups such as African-Americans, Hispanics, Asian Pacific Islanders, and Native Americans.⁽¹⁶⁾ The socialization of some segments of these populations is not geared to the acceptance of traditional medical care or participation in clinical trials and, therefore, poses a special challenge to the research community.⁽³⁸⁾

Some Hispanic women, in particular, constitute a high-risk group because of their social, economic, and citizenship status; their heavy responsibilities as the social, psychological, and financial support for their families; and their high-stress, urban lives.⁽²²⁾ Although there is a dearth of data about the health status of Hispanics, particularly about the distinct subgroups within this population, a number of facts are known:

- Hispanics are the fastest growing population in the United States today.^(22,30)
- The Hispanic population will double in the next 30 years.⁽³⁰⁾
- Hispanics are a young population with a median age of 26.2 years.⁽⁴³⁾
- Hispanics are the least likely population group to have health insurance coverage.^(43*)
- Hispanics experience very high rates of poverty and school dropout.⁽²²⁾
- Teenage Hispanic women have the highest fertility rate in the Nation.^(17,19)
- Hispanics experience very high rates of sexually transmitted diseases, HIV infection, and chronic diseases such as diabetes and hypertension.^(17,19)

A second distinct population of special concern is migrant farmworkers:⁽¹⁵⁾

- There are 3.5 to 5 million women, men, and children who work as migrant and seasonal farmworkers.
- The bulk of these workers—85 percent—are ethnic minorities. Most are Hispanic, but there are also Jamaicans, African-Americans, and Haitians.

- Many experience English literacy and fluency difficulties. A 1989 study reported that 9 out of 10 migrant workers in Wisconsin reported Spanish as their primary language, one-half spoke no English, and 1 out of 4 had not completed the fifth grade (a measure of functional literacy).
- A significant number experience stringent working conditions, inadequate housing, and poor nutrition.
- A 1989 study reported the median family income of migrant and seasonal farm workers to be \$7,330, supporting an average of 5.2 persons per family.
- They live an extremely mobile lifestyle and therefore have limited access to affordable health care, comprehensive health insurance, and other social support services.
- They have the highest infectious disease rate in the United States, high rates of chronic disease, and their risk of HIV infection is 10 times the national average.
- A recent Centers for Disease Control and Prevention (CDC) study indicated that as many as 44 percent of migrant farmworkers test positive on TB skin tests.

There are multiple barriers to recruiting and retaining poor women of color to clinical studies. The barriers are economic, cultural, social, and psychological.⁽³²⁾

These women:

- Lack awareness about available studies.⁽¹⁰⁾
- Often do not understand the purpose of a proposed clinical study or what benefits might result to them personally or to their community from their participation.⁽⁵⁾
- Mistrust researchers and the medical establishment in general because of the gaps in gender, ethnicity, and social and educational backgrounds.^(30,32)
- Are reluctant to be used as subjects of experiments.⁽³⁰⁾
- Have significant logistical problems—lack of child care, lack of transportation, and lack of flexibility about schedules.^(10,30)
- Frequently live isolated lives in rural areas.⁽¹⁰⁾
- Lack the financial ability to pay for treatments associated with a clinical study.⁽¹⁰⁾
- Are reluctant to join a study because they deny a suspected illness or are concerned about issues of confidentiality.⁽²¹⁾

Some Hispanic women experience a number of additional barriers:

- They may be reluctant to participate in a situation where they have to give personal information because of concerns about immigration authorities.⁽³⁰⁾

- They have different beliefs about medicine and follow folk medicine practices.^(45*)
- They may need to receive the permission of a male partner or father in order to participate.⁽³²⁾
- For Hispanic migrant farmworkers in particular, a mobile lifestyle makes participation difficult. For these individuals, “anything that interferes with work is to be avoided.”⁽¹⁵⁾

Recommendations

Numerous recommendations were made about ways to encourage the participation and retention of low-income and minority women in clinical studies.

- Use culturally sensitive/bilingual outreach workers to work with appropriate community groups (e.g., churches, social service agencies, community-based organizations, and local businesses) to discuss potential studies, and to identify and recruit study subjects.^(4,10,17,38,41,43)
- Involve representatives of the study populations in planning the study so as to ensure mutually acceptable decisionmaking.^(10,12,43)
- Design bilingual, culturally sensitive data collection materials, information materials, consent forms, and research methods. These should be concise, at an appropriate reading level, and written in the subjects’ first language.⁽³⁰⁾
- Ensure that study subjects understand the purpose of the study and understand the benefit to them personally and to their community. Help them to develop a pride of ownership in the study.⁽¹⁰⁾
- Include minorities and women in both senior and junior positions on the research team.^(17,43)
- Develop specific ethnic and socioeconomic status indicators to identify accurately Hispanic women, especially distinct Hispanic subpopulations.^(14,19)
- Increase the career opportunities for female and minority scientists.⁽³⁰⁾
- Ensure that study personnel who work with subjects are bicultural/bilingual and sensitive to subjects’ concerns and fears. A mutual relationship of trust, respect, and honesty is crucial.^(30,32,38,43)
- As the study is implemented, ensure that the subjects’ sense of their importance to the study and their personal worth is continually reinforced.⁽³²⁾
- Provide transportation; child care; and expanded, flexible scheduling of visits to research sites.⁽²¹⁾
- Combine elements of the study in one site to increase convenience for subjects.^(10,21)

-
- Conduct aspects of the study in the community itself, for example, in the church social hall, community health care center, or migrant camp.⁽¹⁵⁾
 - Provide culturally sensitive and appropriate incentives for participation.^(4,30)
 - Provide financial coverage for participation in the study.^(24,41)
 - Develop partnerships among communities, their representatives, and research centers.⁽²²⁾
 - Recruit the family, not just the individual, to participate.
 - Build on the stronger concern that many of these subjects have for their children's health rather than for their own. If their children are enrolled in a study, they may be more likely to participate in one themselves.⁽²¹⁾
 - Provide followup to participants and their community once the study is completed by sharing the results and benefits.^(22,43)

It is also recommended that NIH fund a practice-based research infrastructure in migrant and community health centers as an avenue for recruitment and retention of farmworkers and other women of color in clinical studies.⁽¹⁵⁾

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THE OFFICE OF RESEARCH
ON WOMEN'S HEALTH

NATIONAL INSTITUTES OF HEALTH

SCIENTIFIC MEETING:
RECRUITMENT
AND RETENTION
OF WOMEN IN
CLINICAL STUDIES

AGENDA

HOLIDAY INN BETHESDA
BETHESDA, MARYLAND
JULY 12-13, 1993

AGENDA

Monday, July 12

8:30 a.m.

Introduction of Acting Director of the National Institutes of Health

Vivian W. Pinn, M.D.
Director, ORWH

8:35 a.m.

Opening Remarks

Ruth L. Kirschstein, M.D.
Acting Director, NIH

8:50 a.m.

Overview of the Office of Research on Women's Health and Conference Statement

Vivian W. Pinn, M.D.
Director, ORWH

PLENARY SESSION

9:10 a.m.

Overview Statement

Moderator

Shiriki R. Kumanyika, Ph.D., M.P.H.
Pennsylvania State University College of Medicine
Task Force Cochair

9:20 a.m.

Gender Bias in Women's Health Research

Jeri A. Sechzer, M.A., Ph.D.
Pace University

9:40 a.m.

Break

10:00 a.m.

Women's Health Research Legislative and Public Policy Update

Congresswoman Louise M. Slaughter
(D-NY)

10:30 a.m.

Advocacy and Women's Health Research

Leslie R. Wolfe, Ph.D.
Center for Women Policy Studies

10:45 a.m.

Ethical and Legal Issues

Karen H. Rothenberg, J.D., M.P.A.
University of Maryland School of Law

11:00 a.m.

Summary of ORWH Public Hearing on Recruitment and Retention of Women in Clinical Studies

Shiriki R. Kumanyika, Ph.D., M.P.H.
Pennsylvania State University College of Medicine
Task Force Cochair

11:15 a.m.

Discussion

12:00 p.m.

Lunch

PANEL I:

DESIGN AND IMPLEMENTATION ISSUES IN CLINICAL STUDIES

1:30 p.m.

Overview Statement

Moderators

Carol K. Redmond, Sc.D.
University of Pittsburgh
Task Force Member

Julie E. Buring, Sc.D.
Harvard Medical School
Task Force Member

1:45 p.m.

Getting the Job Done in Treatment and Prevention Clinical Trials

■ *AIDS Treatment and Prevention Research*
Melanie A. Thompson, M.D.
AIDS Research Consortium of Atlanta

■ *Cancer Research in Community Settings*
Harry E. Hynes, M.D., Ph.D.
Cancer Center of Kansas

2:15 p.m.

Prevention Studies

■ *Unique Issues for Risk Factor Assessments in Women*
John M. Flack, M.D., M.P.H.
University of Minnesota Hospital and Clinic

■ *Research Considerations Across Diseases and Conditions*
Donna Kritz-Silverstein, Ph.D.
University of California at San Diego

2:55 p.m.

Discussion

3:15 p.m.

Break

3:30 p.m.

Prevention Studies (continued)

■ *Behavioral Modification Studies*
Maureen M. Henderson, M.D., D.P.H.
University of Washington

■ *Cancer Screening*
Dinah K. Pearson, M.H.A.
University of Missouri - Columbia

■ *Contributions of Observational Evidence: Nurses' Health Study*
Charles H. Hennekens, M.D., Dr.P.H.
Harvard Medical School

4:30 p.m.

Discussion

5:00 p.m.

Closing Remarks

Vivian W. Pinn, M.D.
Director, ORWH

5:10 p.m.

Recess

Tuesday, July 13

PANEL II:

PARTICIPANT AND COMMUNITY ISSUES IN RECRUITMENT AND RETENTION IN CLINICAL STUDIES

8:00 a.m.

Remarks: Food and Drug Administration

Ruth B. Merkatz, Ph.D., R.N.
Food and Drug Administration

8:10 a.m.

Overview Statement

Moderators

Barry D. Kaufman, D.M.D.
CBS Radio/Medical News Network
Task Force Member

Helen Rodriguez-Trias, M.D.
American Public Health Association
Task Force Member

8:15 a.m.

Participants' Expectations and Needs

Dyanne D. Affonso, Ph.D., F.A.A.N.
University of California at San Francisco

Patricia A. Ganz, M.D.
University of California at Los Angeles Schools
of Medicine and Public Health

8:45 a.m.

Community Partnerships in Research

Vanella A. Crawford, M.S.W., L.C.S.W.
The Vanella Group

Edwin B. Fisher, Jr., Ph.D.
Washington University School of Medicine

Diane M. Becker, Sc.D., M.P.H.
The Johns Hopkins Center for Health Promotion

Reverend Melvin B. Tuggle
Heart, Body, and Soul, Inc.

Barbara V. Howard, Ph.D.
Medlantic Research Institute

9:55 a.m.

Discussion

10:15 a.m.

Break

10:30 a.m.

Recruitment and Retention of Special Populations

Barbara S. Brown, M.Ed.
Goochland Elementary School
Goochland, Virginia

Elmer E. Huerta, M.D., M.P.H.
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Lee Lee Doyle, M.A., Ph.D.
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Katherine A. O'Hanlan, M.D.
Stanford University Medical Center

11:10 a.m.

Decisionmaking Process

John C. Fletcher, Ph.D.
University of Virginia School of Medicine

11:25 a.m.

Discussion

12:00 noon

Lunch

PANEL III:

INVESTIGATOR AND INSTITUTIONAL ISSUES IN RECRUITMENT AND RETENTION IN CLINICAL STUDIES

1:15 p.m.

Overview Statement

Moderators

Maureen M. Henderson, M.D., D.P.H.
University of Washington
Task Force Member

Marion M. Lee, Ph.D., M.P.H.
University of California at San Francisco
Task Force Member

1:20 p.m.

*Outreach Planning in Designing and Implementing
Clinical Research*

Rodger J. Winn, M.D.
University of Texas M.D. Anderson
Cancer Center

Annlouise R. Assaf, M.S., Ph.D.
Memorial Hospital of Rhode Island

1:50 p.m.

*Benefits and Risks to Investigators and Institutions
in Conducting Clinical Studies*

William R. Hazzard, M.D.
Bowman Gray School of Medicine
of Wake Forest University

2:05 p.m.

*Office for Protection From Research Risks (OPRR)
and Institutional Review Board (IRB) Issues*

Paula Knudson
The University of Texas Health Science
Center at Houston

2:20 p.m.

Discussion

PANEL IV:

CURRENT EXPERIENCES IN WOMEN'S HEALTH RESEARCH

2:45 p.m.

Overview Statement

Moderator
Lewis H. Kuller, M.D., Dr.P.H.
University of Pittsburgh
Task Force Cochair

2:50 p.m.

Women's Health Feasibility Study

W. Dallas Hall, M.D.
Emory University School of Medicine

3:05 p.m.

Postmenopausal Estrogen/Progestin Intervention (PEPI) Study

Valery T. Miller, M.D.
George Washington Medical Center

3:20 p.m.

*Cardiovascular Health Study (CHS) and Women in
Aging Study*

Linda P. Fried, M.D., M.P.H.
The Johns Hopkins Health Institutions

3:35 p.m.

Discussion

CLOSING SESSION

4:00 p.m.

Concluding Remarks

Vivian W. Pinn, M.D.
Director, ORWH

4:15 p.m.

Adjourn

THE OFFICE OF RESEARCH
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THE OFFICE OF RESEARCH
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SCIENTIFIC MEETING:
RECRUITMENT
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CLINICAL STUDIES

LEGAL AND
ETHICAL ISSUES

HOLIDAY INN BETHESDA
BETHESDA, MARYLAND
JULY 12-13, 1993

LEGAL AND ETHICAL ISSUES

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Legal Considerations

Federal Statutes, Regulations, Guidelines and Policies

The applicable federal human subjects regulations, guidelines and policies are: the Department of Health and Human Services (DHHS) protection of human subject regulations,¹ the December 1990 NIH Memorandum (containing the NIH policy for inclusion of women and minorities in study populations), and the NIH Revitalization Act.² The NIH Revitalization Act requires the inclusion of women and minorities in clinical research trials where appropriate. They may be excluded if inclusion would be inappropriate with respect to the health of the subjects, the purpose of the research, or other such circumstances as the Secretary (DHHS) may designate. Regulations are currently being written to implement this act. The 1977 FDA Guidelines (“General Considerations for the Clinical Evaluation of Drugs”) are currently being significantly revised to recognize that women should be included in clinical trials, although FDA policy with respect to pregnant women is still to be developed. It should be further noted that it was anticipated that these 1977 guidelines would be re-reviewed approximately every 18 to 24 months and that no such timely re-review had been made until this past year. The NIH Memorandum and FDA Guidelines are not regulations, but rather guidelines and policies. All have problems of ambiguity.

For example, subpart B of the HHS regulations (which has not been changed since 1975) requires partner consent (absent a few exceptions) when research on pregnant women is for the benefit of the fetus, but not when research is for the “health needs of the mother.” Such terminology is not defined.

The NIH policy concerning the inclusion of minorities and women in study populations, described in the 1990 NIH Memorandum, also has ambiguous provisions. The policy specifically allows exclusion of women from study populations on the basis of a “clear, compelling rationale.” An example of such a rationale is that the study presents an “unacceptable risk for women of childbearing age.” Again, this terminology is not defined. Information from NIH on the justifications deemed acceptable in practice is needed.

Common Law: Tort Liability

There are two basic relevant tort principles: strict liability and negligence. Under the principle of strict liability, if you have an unreasonably dangerous product or activity and it causes injury, you can be liable for that injury even without proof of fault. (Proof of causation, however, is required.) Comment k to Section 402A of the Restatement (Second) of Torts [a compilation listing general rules of torts] specifies that the principle of strict liability will not generally be applied with respect to a drug or vaccine if there is a warning of the drug or vaccine's known *and* foreseeable side effects. The issue arises if it is possible to give informed consent in the situation where there are no data applicable to women of childbearing potential in any of the phase I or early phase II clinical trials.

Under the principle of negligence, a plaintiff must show that the defendant owed the plaintiff a duty of care, the defendant breached that duty (often a battle of plaintiff and defense experts), the plaintiff was injured, and the defendant's breach of the standard of care was the cause of injury. Causation is difficult for the plaintiff to prove. Often, those who are in clinical trials are not healthy, making it even more difficult to prove that a particular drug caused an injury. Perhaps there are not more of these types of cases because causation is difficult to prove, or because informed consent has been adequate.

Notwithstanding sufficient informed consent, a difficult question arises about the mother's ability or the potential mother's ability to waive a right of a future child injured to bring a lawsuit against a researcher. To date, there is no case law on point.

In any case, the concern for liability exposure is out of proportion to the reality. Based on reported cases, the liability threat in the area of clinical research has been basically nil. One of the few cases involving clinical research was against the University of Chicago and concerned the testing of DES on pregnant women. The gist of the action was that the class of pregnant women were not told that they were a part of a double blind experiment to determine the effectiveness of DES in preventing miscarriage. The focus of the class action for battery was that the plaintiffs did not give consent to be a part of the experiment and did not have knowledge of the experiment. The court held that the battery claim was proper and the case was settled.

Liability for *exclusion* of women may potentially be greater than liability exposure for inclusion. Current policies stipulate that greater numbers of women be "guinea pigs" during the marketing phase of drugs than the numbers required by policies governing the numbers of women included in phase I trials or when only small numbers of subjects would be exposed to risk. This issue came to the forefront as a result of the controversy surrounding the use of women in AIDS trials. If women are not included in clinical trials, there may be greater liability exposure, since we now know that there may be foreseeable risks to women if drugs are not pre-market tested on them. If the failure to inform study participants of foreseeable risks reaches the level of reckless indifference, punitive damages as well as compensatory damages may be awarded to an injured plaintiff.

Constitutional Issues

A possible constitutional issue has arisen as a result of a recent Supreme Court case, *Johnson Controls*. This was a case brought under Title VII, a Federal law concerning unlawful employment practices. The company, Johnson Controls, had a policy that excluded all women of childbearing age from jobs in the company's battery factory, where there would be potential lead exposure. The Supreme Court determined that this was a violation of Title VII. The company had argued that it was concerned with fetal protection and the prevention of possible lawsuits by affected offspring. One Supreme Court justice wrote that, if in fact, the company knew what the risks were and acted appropriately in sharing them with the woman, and the woman knew what they were and agreed to continue to work, it would be highly unlikely—although not a guarantee—that a court would ever find the company negligent. This is because negligence means falling below the accepted standard at a point in time; negligence does not mean being perfect or being an insurer.

Johnson Controls is not a perfect analogy to the exclusion of women from clinical trials because having a right to a job is not the same as having a *right* to be in a clinical trial. The underlying argument and the public policy, however, may be applicable: that is, are we prepared, as a matter of fairness, to exclude women from the benefits of clinical trials just because they are in their reproductive years? It is reasonable to conclude that the exclusion of fertile women does have the effect of denying women as a class an equal opportunity to benefit from government funded research.³

Areas of Potential Inquiry

- Do the current HHS regulations, together with the NIH Memorandum's guidelines and FDA guidelines, need to be clarified to specify under what circumstances, if any, it is appropriate to exclude women?
- Is liability, in fact, greater for exclusion than inclusion? Manufacturers cannot hide behind a "myth of liability" for inclusion of women in clinical research.
- What are the constitutional limitations following *Johnson Controls*? Is there an equal protection argument, that is, are we treating men and women differently without a reason (whether rational or higher level of scrutiny)? Why they are being treated differently? Why are women of childbearing years being treated differently from other women? Why are pregnant women being treated differently from non-pregnant women, and how do we justify these distinctions?

Ethical Considerations⁴

The three ethical principles highlighted in the works of the National Commission for the Protection of Human Subjects are beneficence, respect for persons (including autonomy), and justice.

Beneficence refers to the obligation of researchers to provide a favorable risk-benefit ratio to their subjects. For both female and male subjects, there is a risk related to their future reproductive health. For future children, there is a risk of harm (of being born with birth defects). When women are excluded as a class from research, all women are at risk from a lack of information about their health needs.

The principle of respect for persons refers primarily to informed consent issues (and also to recruitment, retention, and "compliance" issues). Informed consent has many factors to be considered, including a subject's capacity to give informed consent, the quality of information given, and the voluntariness of consent granted. Compliance issues, in this context, relate to the difficulty women may have in continuing to adhere to the behavior required by the study: namely, not getting pregnant during the course of a clinical trial.

The principle of justice dictates that the burdens and benefits of research be distributed equitably. The burdens of human subject research should not fall unduly on one class or group of persons, and no class of persons should be denied the right to participate as research subjects. Recent feminist conceptions of justice consider the past oppression and exclusion of women from the benefits of research and the need to consider affirmative action for their inclusion.

The ethic of care may also have application to this area. The paradigm of the mother/child relationship and the need for a contextual understanding of a woman's concern for others, including her offspring, should support a strong ethical foundation for trusting the judgment of women to decide whether to participate in clinical research.

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THE OFFICE OF RESEARCH
ON WOMEN'S HEALTH

NATIONAL INSTITUTES OF HEALTH

SCIENTIFIC MEETING:
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LESBIANS IN
HEALTH RESEARCH

HOLIDAY INN BETHESDA
BETHESDA, MARYLAND
JULY 12-13, 1993

LESBIANS IN HEALTH RESEARCH

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Overview: Why Study or Stratify?

DEMOGRAPHICS NOT KNOWN

A comparison of data from three lesbian health surveys (National, n = 1,925,¹ Los Angeles, n = 330,² and Michigan, n = 1,681³), a lesbian and gay drug use survey⁴ and three national surveys (the National Health Interview Survey,⁵ the National Health Study on Drug Abuse⁶ and the National Health and Nutrition Examination Survey⁷) suggests that there are important epidemiologic differences between lesbians and heterosexual women.

- Lesbians may smoke more.^{1,5}
- Lesbians may be more likely to use/abuse alcohol.^{4,6}
- Lesbians may have higher body mass index.^{1,7}
- Lesbians definitely have higher oligoparity, nulliparity rates.^{1,2,3,8}

- Lesbians may obtain fewer screening exams.^{3,5,9}

For example:

- blood pressure
- breast exam
- pap smear
- mammogram
- stool blood

- Lesbians may have lower rates of self-care.^{1,5}

For example:

- breast self exam
- skin exam
- other (present to M.D. for spotting, pain)

If the above demographic is correct, in comparison to all women, lesbians would then have a higher risk/morbidity/mortality from:

- Breast Cancer
- Lung Cancer
- Ovarian Cancer
- Endometrial Cancer
- Colon Cancer
- Cervical Cancer
- Heart Disease and Stroke.

What is needed is a single large epidemiologic study which will confirm or negate the above suggestions. The Women's Health Initiative (n = 160,000) can provide this in the baseline questionnaire.

ACADEMIC RESEARCH STANDARDS

Blending data from two distinct populations sways results for all and renders the smaller population invisible, potentially leading to inappropriate testing, incorrect diagnosis, and ineffective therapy. Screening programs may not be targeted to the population at greatest risk.

STATED OBJECTIVES OF THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

Public Hearing Summary Draft, May 27, 1993: These standards, originally written to apply to all women, should, in addition, be specifically applied to lesbians. For example:

1. "Research into diseases, disorders, conditions unique to or more prevalent in [lesbian] women."
Lesbians are a marginalized group that does not readily or regularly access the health care system. Historically, lesbians have been alienated from the health care system by health care providers' hostile attitudes toward them. Ample documentation exists describing discriminatory attitudes by physicians,¹⁰ nursing personnel¹¹ and medical students.¹² All of the survey data^{1,2,3,12} confirm that lesbians perceive this and subsequently access the health care system less often, frequently with fear that they are receiving inferior care because of hatred for homosexuals.^{13,14}
2. "To ensure that [lesbian] women are appropriately represented in biomedical and biobehavioral research studies and clinical trials suggested by NIH".
3. "Direct initiatives to increase the numbers of [lesbian] women who are participants in biomedical research careers."
4. "[Lesbian] women cannot expect to gain equitably from new advances in therapy and interventions if they are not included in the clinical trials that ascertain safety and efficacy."

Defining Lesbians in Socio-Political Constructs for Epidemiologic/Demographic Profile

HOUSEHOLD ENUMERATION STUDY

The only way to generate a true demographic profile is to classify dwellings by occupants and pick randomly among those households with single or double female occupancy as the National Census 1990 and the National Health Interview Survey describe for their studies.

This technique locates the broad diversity of lesbians and includes marginalized lesbians, those who are not "out," have low income, are illiterate, or are women of color. It is more expensive, but provides the sensitivity and human contact necessary for accuracy, and most importantly will confirm whether data are applicable to the general population.

DEFINING BY BEHAVIOR

A woman whose sexual behavior ranges from exclusive sexual experience with women to bisexuality, and may include situational experience with males. For example:

In general, if and when you are sexual, do you have sex with:

- a) men
- b) women
- c) both
- d) neither.

- Requires no labels.
- Most women ARE very comfortable answering this.
- Is an objective question which can be seen as appropriate and non-threatening in a scientific health questionnaire.
- Misses the socio-cultural identity and support systems which impact behavior.
- Probably more accurate for demographic profile.

DEFINING BY IDENTITY

A woman whose erotic desire, emotional, social and affectional orientation are toward other women may be defined as lesbian. Most of these women are raised as heterosexuals, repressing their feelings towards other girls in childhood, until coming to reckon with these feelings at some later age. Some have never had sex with males; some have married and borne children; some are situationally sexual with males due to economics, cultural factors or sexual desire, and may or may not culturally identify as lesbians. For example:

In general, do you identify yourself as:

- a) heterosexual
- b) bisexual
- c) lesbian, gay, homosexual
- d) don't know, none of the above.

- Requires an individual to categorize herself by self-concept.
- May be inaccurate over time.
- Terms not used by all (some lesbians will not use this term for themselves).

- Some women identify more with race/ethnic group and not so strongly by sexual orientation.

IDENTITY VERSUS BEHAVIOR—TENTATIVE CONCLUSIONS

Both questions are important and should be included in all studies to generate data until such profiles have been delineated which show important differences. Behavior questions should be in a behavior section: for instance, in the first half of a questionnaire, separate from an identity question in the self-conceptual section, or at the end of the questionnaire.

Behavioral questions are always more important in the medical exam and should always be included in any survey as a minimum investigation into this area. It is recommended that the research team write a behavioral question that reflects an understanding of the population to whom the survey will be administered.

Recruitment of Lesbians into Health Research

SAFETY ISSUES

Some lesbians, fearing for their job, their reputation, or their safety elect to hide their orientation and require anonymity. It is important to reassure them of the reasonable limits of research confidentiality. Show a willingness to share results with subjects and reassure them that lesbians have been involved in the writing of the project and analysis of data. Include “out” lesbians in all staff and research levels.

LOGISTICS

- Clinical research staff should include lesbians, lesbians of color, and reflect the lesbian community in general.
- Recruitment efforts in the general lesbian community should include:
 - Advertisements in lesbian newspapers, organizations, bookstores, clinics, metropolitan community churches. Expect lesbian-specific posters to be stolen; it is necessary to replace them frequently.
 - Obtaining endorsements of advertisements by lesbian community leaders, lesbian clinics, or lesbian-friendly health care providers.
 - Informants, that is, members of the community with whom a personal relationship is established and who allow their names to be used in recruiting, can serve as potential interviewers and give feedback on instrument.

- Use of lesbian clinics as sites.
- Establishment of a local lesbian advisory committee for further advice.
- Issues in recruiting lesbians of color:
 - Some suggest recruiting first only lesbians of color. It is often recommended that the goal should be greater than or equal to 50% people of color. “Especially invited” does not work.
 - Sending posters to ethnic/race organizations.
 - Reassuring people of color of the benefits to them and their community of this research. Don’t “rip off” data.
 - Use of informants and attendance at meetings with people of color to describe research.
- Recruitment of low-income lesbians should include:
 - Advertisements specifically for low-income lesbians. Place posters in government assistance offices, methadone clinics, homeless shelters, soup kitchens, grocery stores, emergency rooms.
 - Pay incentives and/or free lab tests.

Retention

Important issues include:

- Ensuring continuity of clinic staff, female staff, staff sensitive to lesbian issues, comfortable with lesbians.
- Continuing to reassure participants that their community will benefit from the research.
- Showing appreciation for their commitment to research progress.
- Keeping in contact with substance abusers, low-income women, and HIV positive women, all of whom may need more frequent contact.
- Providing ongoing pay for appointments.

Instrument

USE GENDER NEUTRAL TERMS

“Partner,” not “husband.” Use neutral pronouns or “he/she” and “her/him.”

CULTURALLY SENSITIVE

All questions with respect to race/ethnicity/lesbian orientation must be framed in a culturally sensitive way. A culturally sensitive instrument can encourage collaboration with lesbians, people of color, researchers in areas of race/ethnicity and sexual orientation. Obesity is a controversial issue for lesbians; rather than ask about it, simply calculate body mass index from measured height and weight.

QUESTIONNAIRE FORMAT

The interviews should be conducted preferably by a female interviewer, face-to-face, to maximize information from lesbians of low income and lesbians of color.

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