Politics and Clinical Trials: The Inclusion of Women

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INTRODUCTION

Prior to the third quarter of the 20th century, the Food and Drug Administration’s (FDA’s) guidelines for the inclusion of women in clinical studies for all types of illnesses were limited. The FDA barred women of childbearing age from all phase I trials (safety studies) and from all other studies until animal teratology and fetal toxicity studies could be completed and analyzed.

After the U.S. Public Health Service Task Force on Health deemed that excluding women from clinical research was detrimental to women’s health, guidelines from the National Institutes of Health (NIH) urged the inclusion of women in NIH-sponsored research. The NIH Revitalization Act mandated that the NIH ensure that women and members of minority groups be included in all research on humans. The U.S. General Accounting Office (GAO), however, stated that the FDA was not thoroughly monitoring research data to determine how sex differences were affecting the safety and effectiveness of medicine.

Although it was slow at first, progress in including women in clinical trials has followed the changes in health care policies and regulations over the past quarter century. Many drug therapies and their effects on women need to be reassessed. Although the regulatory agencies did adopt some important federal rules and regulations, it was not until late in the 20th century that study protocols included women in a meaningful way.

CHRONOLOGICAL PERSPECTIVE 1960–1970s

In the early and middle 20th century, women’s participation in clinical studies of new drugs was minimal. Their under-representation stemmed from the belief in the federal government and its agencies that it was not safe to study the safety and efficacy of new drugs in women.1,2 It was their way of protecting female subjects, especially those of childbearing age, from reproductive problems that might result from testing new chemical entities. Drug testing was encouraged in men, and it was assumed that whatever safe and effective doses were derived from clinical studies in men could be extrapolated for women.

Of course, the thinking was totally fallacious; it was not until the 1970s that the FDA realized that federal legislation, up to that decade, was not offering the same quality of drug care to women that was offered to men. The political climate, as a result of the women’s movement in the U.S., was beginning to change along with the realization that clinical research on the effects of new drugs on people was not being conducted in an ethical manner if at least half of the population was being excluded.

In 1964, the World Medical Association affirmed and adopted the Declaration of Helsinki as a statement of ethical principles to guide physicians and other participants in medical research involving humans.3 In medical research on human subjects, considerations related to their well-being had to take precedence over the interests of science and society. Medical research was subject to ethical standards that required respect for all people and that protected their health and rights. Healthy volunteers were precluded, and the research was to be conducted only if the importance of the objective outweighed the inherent risks and burdens to the patients.3 Every biomedical research project involving humans was to be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to patients or to others. The Declaration of Helsinki contained no statement excluding women from biomedical research.3

In 1975 in the U.S., the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research4 passed a special regulation, the Belmont Report, which described the principles of equitable selection of research subjects. Congress established the Commission (1974–1978) under the National Research Act: Public Law 93-348, Title II, Part A, on July 12, 1974. The Commission’s purpose was to conduct a comprehensive investigation and to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving humans in the U.S. The Commission developed guidelines to ensure ethical research protocols.5

The Commission undertook a comprehensive study of the ethical, social, and legal implications of advances in biomedical and behavioral research and technology.5 One of the principles was the justice involved in the selection of research subjects. Justice was considered to be relevant at both the individual level and the social level.4

- Individual justice required that researchers exhibit fairness in (1) not offering potentially beneficial research to only some patients and (2) not selecting only “undesirable” persons for risky research.
- Social justice required that a distinction be drawn between classes of subjects (e.g., adults and children) who should and should not participate in a particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already troubled persons. Thus, it was considered a matter of social justice that there be an order of preference in selecting classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., institutionalized mentally infirm patients or prisoners) might be research subjects only under certain conditions. The Commission did not distinguish, in patient selection, on the basis of sex.

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This principle of distributive justice was applied to the equitable selection of research subjects. For example, if women were going to acquire the benefits of the particular research, such as the use of new drugs or devices, they had the right and the responsibility to participate in the research. Because of the sensitivity of clinical research in 1974 and 1975, however, the Commission members approved some special regulations that were promulgated in 1975 to provide extra protections for vulnerable subjects undergoing research, such as children, mentally disabled people, educationally disadvantaged persons, prisoners, and pregnant women. In regard to pregnant women, the fetus—not the mother—was considered to be the vulnerable subject. Unfortunately, the only definite way to protect fetuses was to exclude all women from research.

In 1977, the FDA recommended that premenopausal women who were capable of becoming pregnant be excluded from early drug studies. Even though the FDA guidelines referred to early phases of drug development, the Pregnancy Discrimination Act of 1978 affected the participation of women in all phases of trials. The Act stated that women who were pregnant or who had pregnancy-related conditions had to be treated the same as other applicants and employees with regard to their ability or inability to work. However, following the tragedies caused by the use of thalidomide and diethylstilbestrol in pregnant women, the FDA’s guidance in 1977 recommended against including women of childbearing age in the early phases of drug testing unless the study concerned life-threatening illnesses.

1980–1990s

In 1981, the National Commission, in describing the principles of equitable selection of subjects, stated that women could take part in all research studies. This decision coincided with a publication by Kinney et al. showing that young women served as subjects in premarketing drug trials less frequently than young men. The authors discussed the moral, legal, and medical implications of women’s underrepresentation and the increased risks to female patients because of the denial of medication. Furthermore, safety risks increased when women received certain new drugs only in the postmarketing phase.

It was not until 1991 that 16 federal departments and agencies adopted a single, general set of regulatory provisions governing protections for human subjects. The Common Rule specified how research involving humans was to be conducted and reviewed, including the rules for obtaining informed consent. The Common Rule was developed in response to recommendations made by the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research back in 1981, calling for the adoption by all federal agencies of the U.S. Department of Health and Human Services (DHHS) regulations then in effect to protect human research subjects. The DHHS specified additional protections, as part of the Common Rule, for research on certain populations: pregnant women, fetuses, and patients involved with in vitro fertilization research, prisoners, and children.

Although the NIH supposedly addressed the systematic exclusion of women from clinical research in 1986 by adopting a policy requiring their inclusion, a GAO report in 1990 revealed that women were still being excluded from many clinical studies. This led to a public outcry and political pressure that helped secure the establishment of NIH guidelines to include women and minority groups in clinical trials as part of the NIH Revitalization Act of 1993 (Public Law 103-43).

First, the Office of Research on Women’s Health, dedicated to the improvement of women’s health in America, was established in 1990 as part of the NIH. In 1994, the FDA created the Office of Women’s Health (OWH), which established a new chapter in the agency’s commitment to women’s health issues. The Office was concerned with federal policies and public laws regarding the inclusion of women and minorities in clinical research and promoted research directed toward women. The goals were to strengthen, develop, and increase research into diseases, disorders, risk factors, and conditions that were unique to, more prevalent among, or more serious in women.

The 1993 NIH Revitalization Act guidelines demanded the inclusion of women and members of minority groups in all NIH-supported biomedical and behavioral research projects involving human subjects. In investigations of new drugs or therapies, women were included in only approximately 50% of the studies. The Act allowed the restriction on women of childbearing age to be lifted to allow them in early-phase clinical trials. Unless a clear and compelling rationale and justification established that inclusion was inappropriate because of the subject’s health or the purposes of the research, women and minorities had to be included in the studies.

To ensure the inclusion of women in clinical research, new FDA guidelines in 1993 eliminated the earlier policy that had virtually banned women with childbearing potential from entry into the early phases of clinical trials. The guidelines also called for an analysis, by gender, of the safety and effectiveness of drugs and biologicals and identified broad areas of interest in relation to sex-specific factors in responses to drugs. The gender guidelines focused on data needed for drug approval and marketing, with only limited reference to the details of drug development or when and how to study both sexes. Although the guidelines did not require the early participation of women, they indicated that their participation would be of value.

The need to include both women and men in clinical studies was substantiated by analyses of unpublished data from 26 bioequivalence studies submitted to the FDA that showed significant gender differences in approximately 28% of the data sets. Where data variability (areas under the plasma concentration–time curve [AUC] and maximum concentration [Cmax]) differed between the sexes, it was suggested that higher variability in women (within the subgroup) might be more common and that a sex-based subject-by-formulation interaction could occur, although perhaps with low frequency.

Sex-related differences in pharmacokinetics were apparent in the many drugs studied. Dosage adjustment according to body weight may be necessary for drugs that exhibit a steep dose–response curve. Although this study was exploratory, the results supported the FDA’s recommendation in 1993 that women not be excluded from bioequivalence studies.

Following publication of the new gender guidelines in the 1990s, subsequent statistical evaluation of all NIH phase III (extramural) clinical trial studies showed that women repre-
sent 67.2% of the enrolled subjects in 1998 and 74.8% of the enrollees in 1997.17 Earlier phase III NIH (intramural) studies had included fewer women.17

2000s

Supplementary federal legislation was proposed in October 2001 for the additional protection of human research subjects.18 The NIH adopted the definition of “clinical” research as patient-oriented (i.e., it was conducted with human subjects for which an investigator [or colleague] directly interacted with them). Patient-oriented research included mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies, epidemiological and behavioral studies, and outcomes research.

Language governing NIH-defined phase III clinical trials was clarified to be consistent with the mandate for the inclusion of women and minorities as subjects in clinical research (Public Law 103-43),18 the new Public Health Service 398 Form, and the Office of Management and Budget (OMB) Directive 15.18

THE WOMEN’S HEALTH INITIATIVE

Conjugated equine estrogens and medroxyprogesterone have been the most commonly prescribed postmenopausal hormone therapy in the U.S. for women with a uterus and, until 2001–2002, had been used each day by more than six million women.19 It had been thought that the use of these agents would prevent cardiovascular disease, osteoporosis, and cancer in postmenopausal women during the aging process.

To confirm this theory scientifically, Congress mandated and the NIH established the Women’s Health Initiative (WHI) in 1991 to address the most common causes of death, disability, and impaired quality of life in postmenopausal women.20 The WHI, a 15-year, multimillion dollar endeavor and one of the largest U.S. prevention studies of its kind, addressed cardiovascular disease, cancer, and osteoporosis. The major components of the WHI20 were:

1. a randomized, controlled clinical trial of promising but unproven approaches to preventing disease.
2. an observational study to identify predictors of disease.
3. a study of community approaches to develop healthful behaviors.

The overall goal was to reduce coronary heart disease, breast and colorectal cancers, dementia, and osteoporotic fractures in postmenopausal women by using preventive strategies and identifying risk factors.

Women who had been randomly selected to receive active hormones were taking conjugated equine estrogens 0.625 mg each day and medroxyprogesterone acetate (progestin) (Prempro19, Wyeth) 2.5 mg each day.21 On May 31, 2002, the 10th interim analysis was conducted. At that time, the use of conjugated equine estrogens and medroxyprogesterone was observed to be associated with an increased risk of breast cancer. The additional findings of excess heart disease, stroke, and pulmonary embolism outweighed the evidence of the benefits.

It was concluded that the estrogen–progestin combination did not prevent heart disease in these women.22 For women taking the hormonal combination, the risks (increased breast cancer, heart attacks, strokes, and blood clots in the lungs and legs) outweighed the benefits (fewer hip fractures and colon cancers). After the WHI study results were published in 2002, an estimated 3 million women in the U.S. (a 50% decline) were taking the combined hormones.22

During the first four years of the WHI, there was no difference in the rate of breast cancer development between women taking estrogen plus progestin and those taking placebo. After that time, the numbers began to increase; after an average of 5.2 years, the risk of breast cancer in healthy postmenopausal women taking estrogen–progestin therapy increased, compared with women taking placebo.23 Thus, the risk–benefit profile found in this trial was not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results suggested that this drug regimen should not be initiated or continued to prevent coronary heart disease.21

In the WHI substudy of memory, older women who were taking combination hormone therapy had twice the rate of dementia, including Alzheimer’s disease, compared with women who were not taking the medication.23 In a study of women aged 65 and older, the risk of dementia was heightened in those who took estrogen–progestin therapy. This combination did not protect against the development of mild cognitive impairment, a form of cognitive decline that is less severe than dementia. Because of these newer findings, the National Institute on Aging recommended that combination hormone therapy should not be prescribed for older postmenopausal women to maintain or improve cognitive function.

CONCLUSION

The old cliche “You’ve come a long way, baby” is more meaningful in the world of medical research for women today than it has been in the last 100 years. Until recently, medical research has largely ignored many health issues important to women, and women have long been underrepresented in clinical trials.

In the past, research on women’s health focused on diseases that affected fertility and reproduction, whereas many studies on other diseases focused exclusively on men. Today, most women receive diagnoses and treatment based on what has proved to be effective for men. However, the political efforts of women’s health advocates, the general public, and the unveiling of inequities in medical research have led to a broadened research agenda. Federal intervention and congressional legislative rules have begun to level the playing field. Research is beginning to yield insights into the health-related similarities and differences between men and women.

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