

Inclusion of Women in Clinical Trials: A Historical Overview of Scientific, Ethical, and Legal Issues

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During the past 20 years, there has been a dramatic shift in scientific, ethical, and legal perspectives regarding the inclusion of women in clinical trials conducted in the United States. A historical overview of why women previously were excluded from clinical trials is presented, and the reasons for current policy changes are discussed. The clinical necessity for testing drugs in specific populations (e.g., women) to ensure appropriate dose regimens and to minimize the likelihood of adverse effects is discussed. The difficult issue of prescribing drugs for pregnant women is highlighted. *JOGNN*, 27, 78-84; 1998.

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The U.S. Food and Drug Administration (FDA) reviews findings from clinical trials conducted by pharmaceutical companies and other sponsors to determine whether new medical products are sufficiently safe and effective to be marketed to the public (Drug Amendments, 1962; Pure Food & Drug Act, 1938). In 1977, the agency issued a guideline for the clinical evaluation of drugs that called for the exclusion of "women with childbearing potential," from the early phases of most clinical studies (U.S. Department of Health, Education and Welfare [US HEW]: Food & Drug Administration [FDA], 1977). The phases of drug development, when basic issues of safety, dose ranging, and efficacy are evaluated, are shown in Figure 1. The exclusion was applied broadly to include premenopausal women capable of becoming pregnant, except women with life-threatening diseases. This ban was implemented in the protectionist climate that had developed and subsequently prevailed after birth defects were found to be as-

sociated with the maternal use of certain drugs, such as thalidomide. The consensus of ethical opinion at the time was that the potential for any fetal risk was unacceptable in studies that might not have important direct medical benefits to the participating subjects.

During the past 20 years, both scientific and ethical perspectives regarding the inclusion of women in clinical trials of new biomedical products have shifted dramatically. Including women with childbearing potential in the early phases of trials has been shown to have scientific advantages, and it has been acknowledged that the potential for fetal risk can be reduced by attention to protocol design. Current ethical principles demand respect for women's autonomy and decision making capacity. As a result, the FDA has promulgated new policies that have modified significantly the 1977 FDA guideline and have reversed the ban on inclusion of women. Such policy changes have been mirrored at the National Institutes of Health (NIH), the premier federal government locus of biomedical research. In response, sponsors of research such as pharmaceutical companies have begun to modify their policies and practices for inclusion of women in clinical trials. This article traces the pivotal events leading to this important paradigm shift.

The Historical Framework

The past several decades have seen increased national attention focused on issues relating to women's health. Seeds planted in the women's movement of the 1960s and 1970s began to bear fruit in the 1980s when the U.S. Public Health Ser-

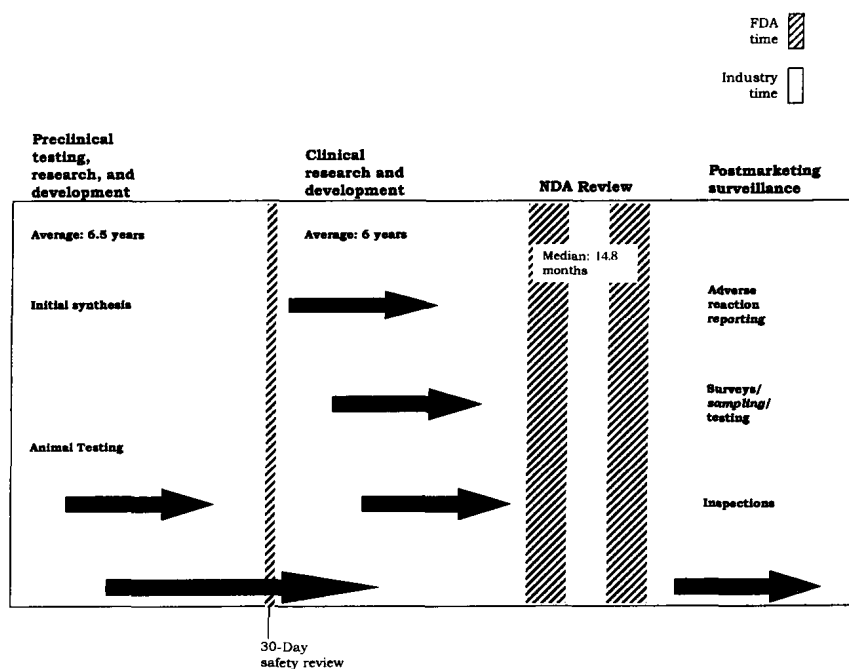


FIGURE 1
New drug development timeline.

vice established a task force on women's health. The task force concluded that a longstanding lack of research in women's health had compromised the quality of available information on diseases affecting women and the health care women receive (US DHHS: Public Health Service, 1984). Among the suggestions that were made to redress these problems, the task force recommended that steps be taken to assure the broader and fuller participation of women in clinical trials.

In response, the NIH issued a policy in 1986 designed to encourage inclusion of women in clinical research supported by federal funds. However, 4 years later the U.S. General Accounting Office (GAO) found that the NIH had made little progress with respect to implementing its policy (US GAO: NIH, 1990). Criticism mounted, and the Congressional Women's Caucus turned to legislative action. A package of bills known collectively as the Women's Health Equity Act of 1990 was enacted and became a legal force around which women's health advocates began to mobilize. In 1990, responding to this new legislation, the NIH created an Office for Research on Women's Health to ensure that women's health research is an integral part of the scientific fabric at NIH and throughout the scientific community.

Attention to the inclusion of women in clinical trials also emerged from an increased scientific appreciation for the value of understanding how drugs and other therapies work in specific patient groups. Many factors can influence drug responses in people, including age, gender, race, and concomitant diseases. Other variables, especially those resulting from differences in body size, extent and distribution of body fat content, hormonal

environment, or enzyme production important to metabolism also are important (Merkatz et al., 1993). Any of these influences or combinations of them can alter the choice of a medication, its dose, or the interval at which it is prescribed. For example, certain cardiovascular drugs, such as propranolol, are metabolized more slowly in women, and other therapeutic agents such as acetaminophen, lidocaine, and aspirin have lower rates of clearance from the body in women than in men (Harris, Benet, & Schwartz, 1995). Hormonal variations associated with the menstrual cycle, menopause, oral contraceptive use, or estrogen supplementation may result in differing drug effects that warrant elucidation. Such information may be especially important for drugs that have a narrow therapeutic range (i.e., the range of dosing to achieve a therapeutic, rather than a toxic, effect is narrow).

As the value of individualizing treatment for population subgroups gained recognition, the FDA became concerned that drugs were not being tested in the full range of patients who eventually would receive them (Sherman, Temple & Merkatz, 1995). In a 1983 survey of 11 pending new drug applications, the agency found substantial enrollment disparities, with women and the elderly significantly underrepresented in some disease study categories, including cardiovascular studies (data published in US DHHS: FDA, 1993). Subsequent surveys, undertaken by the FDA's independent researchers revealed similar findings (US DHHS: FDA, 1993). Although the 1977 FDA guideline had excluded women of childbearing potential only from the first and the earliest part of the second phase of clinical trials (when drug

safety is the primary focus), sponsors often interpreted the restriction more broadly and limited entry of women into the later phases of drug trials.

The FDA recognized that a failure to include sufficiently diverse populations in trials for new drugs could erroneously lead to treatment protocols skewed toward a norm of middle-aged, white males. Thus, in 1988 the agency issued a guideline that specifically called for analyses of safety and efficacy data by gender, age, and race (DHHS: FDA, 1988). However, a subsequent study published by the GAO, covering the period from 1988 through 1991, showed that only about half of the clinical trials examined had been analyzed for gender-related effects (US GAO, 1992). Women still were underrepresented significantly in disease categories such as heart disease (US GAO, 1992).

Twenty years ago women of childbearing age were excluded from participation in the early phases of clinical trials for most drugs.

The human immunodeficiency virus (HIV) epidemic provided another forceful influence on efforts to include women in clinical trials. Especially in the early days of the epidemic, when few effective treatments had been developed, participation in clinical trials represented the greatest hope for receiving a new effective treatment. However, according to the AIDS Service Center of the HIV Law Project, as of January 1992, only 1,151 women had been included among the 14,799 participants enrolled in the AIDS Clinical Trials Group studies sponsored by the National Institute of Allergy and Infectious Diseases (Pearl, Banzhaf, Leger, & Long, 1992). Such a finding was the impetus behind a citizen petition filed by the HIV Law Project, together with the NOW Legal Defense and Education Fund, the AIDS Project of the American Civil Liberties Union, and other community-based HIV organizations urging the FDA to remove its exclusion on women with childbearing potential. They urged that women be permitted to determine for themselves whether or not to enter a clinical trial and that the 1977 guideline be replaced with a standard that emphasized informed consent (HIV Law Project, 1992).

At the same time, the ethical perspective about participation in clinical trials was evolving from an earlier primary focus on protecting vulnerable populations to one that emphasized autonomy for potential subjects. The National Commission for the Protection of Human

Subjects of Biomedical and Behavioral Research (1979) defined three ethical principles that should govern research: beneficence, justice, and respect for persons. The principle of beneficence, according to the Commission, required not only that subjects be protected against risk of harm but also that society be concerned about a loss of substantial benefits that might be gained from research. Later interpretations of these principles (the Belmont principles) concluded that justice is best served when medical research benefits both men and women equally (Institute of Medicine, 1994; US DHHS: FDA, 1993). Application of the justice principle also requires that therapeutic interventions be adequately tested in populations for whom they are to be ultimately used. The argument also was advanced that respect for persons enables informed individuals to assume certain risks and that excluding informed individuals without considering their wishes diminishes their autonomy (Institute of Medicine, 1994).

The landmark case of *United Automobile Workers v. Johnson Controls* also had an important influence on ethical and legal perspectives related to issues of exclusion by gender (*International Union, United Automobile, Aerospace and Agricultural Implement Workers of America, UAW, et al v. Johnson Controls*, 1991). In a 1991 decision, the Supreme Court ruled that, under the terms of the Pregnancy Discrimination Act (1978), pregnant women could not be excluded from employment solely because their working conditions posed a potential fetal risk. Although significant distinctions exist between employment rights and participation in clinical trials, the court's decision gave additional weight to the growing consensus about the importance of autonomy and informed consent. The constitutionality of excluding women from government-funded research was challenged. Others argued that this challenge could apply even to privately funded trials authorized by the FDA because the agency is part of the federal government. Specifically, some have contended that exclusionary policies in research deny equal opportunity to women as a class and can not be justified in light of the benefits that accrue to men (Charo, 1994; Merton, 1993; Rothenberg, 1996).

Still another defining event was a report from the Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies (Institute of Medicine, 1994). Convened at the request of the NIH, this Committee was notable for the breadth of its representation and for the scope of its recommendations. The 16 members, whose backgrounds included bioethics, law, epidemiology, biostatistics, public health policy, obstetrics and gynecology, clinical research, the pharmaceutical industry, and the social, behavioral, and clinical evaluative sciences, concluded

Women and men should be enrolled as participants in clinical studies in a manner that ensures that research yields scientifically generalizable results applicable to both genders (Institute of Medicine, 1994, p. 5).

Policy Changes Occurring at the FDA and NIH

To ensure that new drugs would be properly evaluated in women, the FDA in 1993 issued its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. Similar to a 1988 guideline designed to encourage the inclusion and evaluation of elderly patients in clinical trials (DHHS: FDA, 1988), the agency called for a "reasonable" number of women to be included in new clinical trials. It emphasized the need to assess possible pharmacokinetic differences—differences in drug concentrations in the blood or other tissues by gender. It called for pharmacodynamic studies to assess the body's response to a given concentration of a drug when efficacy, rates of adverse events, and dose response differed by gender. Examination of drugs relative to women's natural hormonal milieu was suggested, as were drug interaction studies with hormonal contraceptive agents and hormone replacement therapy. At the same time, the guideline articulated the agency's decision to reverse the 1977 policy that had effectively barred most women of childbearing potential from participating in the earliest phases of clinical trials.

A new scientific interest in women's health led the FDA and NIH to review their policies and ultimately change their positions about the inclusion of women in clinical trials.

Although the agency's views about protection of a developing fetus from exposure to potentially harmful drugs had not changed, its decision reflects a recognition that alternate mechanisms exist to reduce that risk and that other social good has to be considered (Merkatz et al., 1993). To reduce the risk of inadvertent pregnancies during the course of clinical trials, the agency recommends the use of pregnancy tests under certain circumstances and counseling trial subjects about contraception when appropriate. Institutional review boards, charged with ensuring the ethics and scientific integrity of proposed studies at local trial sites, are expected to scrutinize

trials involving known or potential teratogens with special care.

The impact of the new policies on product liability has not been determined, although historical research suggests that pharmaceutical companies have not faced substantial litigation from individuals who have participated in clinical trials. Liability is more likely to arise when therapeutic products are ultimately prescribed to a population for which there has not been adequate testing (Flannery & Greenberg, 1994). Of greatest concern to industry sponsors of research is the potential liability exposure if problems develop in the child of a woman who has participated in a clinical trial. However, it has been argued that product liability associated with experimental therapy is most likely to arise from elements of negligence or the failure to comply with informed consent regulations, both of which are not gender-specific issues.

New requirements for the inclusion of women and minorities in federally funded clinical trials also were incorporated into the NIH Revitalization Act of 1993, and a year later, a new NIH guideline was jointly issued by the Office of Research on Women's Health and the Office of Research on Minority Health (US DHHS: NIH, 1994). This guideline stipulates that the NIH must ensure that women and members of minority groups and their subpopulations are included in all human subject research. Specifically, they must be included in Phase 3 clinical trials in numbers sufficient to allow a valid analysis of differences in intervention effects. Cost may not be used as a reason for excluding either women or minority groups. Grant proposals being considered by any Institute within the NIH must be reviewed for compliance with this guideline, and funding may be denied if guideline criteria are not met.

Ongoing Efforts to Support Inclusion

The new policies in place at the FDA and the NIH mean that a wider inclusion of women in clinical trials and more detailed gender analyses will become the norm. There are indications that industry has enrolled more women in clinical trials and is doing so earlier in the drug development process (US DHHS: FDA, in press). However, a recent FDA survey of gender analyses being submitted as part of new drug applications highlighted additional steps that need to be taken to maximize the utility of information collected (US DHHS: FDA, in press). Scientists at the FDA are recommending that new drug applications include more complete analyses of safety and efficacy results specifically for men and women. They also suggest that researchers use meta-analyses to maximize the amount of information gained for both genders and consider new ways to think about and perform meta-analyses when pooling information

from studies of varying designs (US DHHS: FDA, in press).

Although progress has been made, women still appear to be underrepresented in some important clinical trials, notably in the area of HIV and acquired immune deficiency syndrome (AIDS). In 1995, the National Task Force on AIDS Drug Development recommended that women with a life-threatening disease not be excluded from any phase of clinical trials, despite the risk or potential risk of reproductive or developmental toxicity from the use of an investigational drug. The Presidential Advisory Council on HIV/AIDS adopted the AIDS Task Force recommendation. In accordance with this recommendation, the FDA has proposed amending its regulations for conducting clinical trials for drugs and biologic products (blood products and vaccines) intended for life-threatening diseases (DHHS: FDA, 1997). Under the new rule, the FDA would be permitted to issue a clinical hold (to stop a proposed or ongoing clinical trial designed to test a new therapeutic product for a life-threatening disease) if women with reproductive potential are excluded from entering such a trial because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug. This new proposed rule provides additional evidence of the marked changes that have occurred during the 1990s in considering the risks and benefits of including women in all phases of clinical trials.

Pregnancy and Clinical Trials

From an ethical and medical perspective, the most sensitive remaining issues involve the question of including pregnant women in clinical trials. Fetal protection has been and remains an essential priority, and liability fears are germane. However, the fact is that most drugs that are used during pregnancy have not been tested in that population. In addition, few opportunities have been created to collect postmarketing surveillance data on the substantial medication use that is prescribed for pregnant women.

Most drugs used routinely in pregnancy have not been tested on pregnant women.

In November 1994, the FDA's newly created Office of Women's Health held a workshop that explored questions relating to the use of FDA-regulated products and

pregnant women (US DHHS: FDA, 1994). The workshop chair stated,

Because so few drugs have been well-studied in pregnant women, prescribing medications is generally left to a health provider's individual experience. As a result, the scientific basis to treat women who begin a pregnancy with a chronic disease, or develop a pregnancy-specific medical condition is often inadequate. Moreover, the physiological alterations of pregnancy are rarely considered or addressed in descriptions of standard dosing regimens (US DHHS: FDA, 1994, p. 2).

Nancy Buc, the Conference co-chair, underscored the urgency of the medical need. "We need to know more about which drugs at which dosages in which forms and by which routes of administration are safe and effective in pregnant women" (US DHHS: FDA, 1994, p. 41), adding that this information could be collected only through clinical trials. Dr. Roy Pitkin decried an "attitude of therapeutic nihilism" (US DHHS: FDA, 1994, p. 4), in which pregnant women are likely to be denied indicated therapy for fear of its teratogenic effects. Although such a fear is legitimate, there remains an urgent need to treat pregnant women effectively and, by so doing, to promote better outcomes for infants.

The importance of testing drugs in pregnancy has been demonstrated recently by the NIH-sponsored randomized clinical trial 076, which treated HIV-infected pregnant women with AZT (zidovudine). The study was terminated before its conclusion because of dramatic reductions in the rate of perinatal transmission in the group treated therapeutically (Connor et al., 1994). Newer forms of treatment of HIV infection among non-pregnant individuals have emerged with protease inhibitors and have replaced AZT monotherapy as the standard of care. Perinatologists and other health care providers must again grapple with determining the best treatment regimen to use during pregnancy. They must care for women without benefit of information about use of these new drugs in pregnancy.

Drugs for use in pregnancy are categorized by the letters A through D and X, according to their relative safety and the extent to which testing has been completed (Table 1). Because so few products have been tested in pregnant women, almost none are ranked as Category A. Much more often, they are listed in drug reference manuals as either Category B or Category C.

The absence of data about drug use in pregnant women results in far more questions than answers. The FDA has created a special task force that is examining relevant issues and considering some of the recommendations advanced at its 1994 pregnancy conference. One issue under study is the appropriateness of substituting narrative descriptions for the five-letter categories so that health care professionals and their patients can have

TABLE 1
FDA Use-In-Pregnancy Drug Categories*

Category A: Controlled studies show no risk
Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
Category B: No evidence of risk to human fetus
Either animal findings show risk but human findings do not, or if no adequate human studies have been done, animal findings are negative.
Category C: Risk cannot be ruled out
Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify the potential risk.
Category D: Positive evidence of risk
Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
Category X: Contraindicated in pregnancy
Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefits to the patient.

* The FDA's Use-In-Pregnancy Categories are based on the degree to which available information has ruled out risk to the fetus, balanced against the drug's potential benefits to the patient. From: Specific requirements on content and format of labeling for human prescription drugs. 21 CFR 201. 57(F) (6).

more information about what is known regarding use of a drug in pregnancy. The agency also is considering how the preclinical animal studies can best be designed to predict human fetal risk more accurately and under what circumstances trials should be conducted in pregnant women. The use of postmarketing surveillance to secure better data on how medical products work in pregnancy is another suggested means of acquiring information. Debate about when and under what situations pregnant women should be included in clinical studies, either premarketing or postmarketing, will continue for some time to come.

Conclusion

Promoting research and disseminating information about how drugs work in women throughout the life span is an important issue for nurses, who often are the primary health care professionals advising patients about their medications. Nurses must be familiar with what is known and what is not known and educate their patients accordingly. Nurses should consider this critically important issue as a research priority, and promote, collaborate, or conduct research that will add to know-

ledge about how drugs work in women. Nurses also must take an active role in formulating local and national policy about the inclusion of women in clinical trials. Such policies ultimately affect the health and well-being of women.

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