



DIGITAL ACCESS TO SCHOLARSHIP AT HARVARD

FROM PROTECTIONISM TO ACCESS: WOMEN & PARTICIPATION IN CLINICAL TRIALS - CONFLICT, CONTROVERSY, AND CHANGE

The Harvard community has made this article openly available.
[Please share](#) how this access benefits you. Your story matters.

Citation	FROM PROTECTIONISM TO ACCESS: WOMEN & PARTICIPATION IN CLINICAL TRIALS - CONFLICT, CONTROVERSY, AND CHANGE (2002 Third Year Paper)
Accessed	February 19, 2015 9:36:46 AM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:8889449
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)

FROM PROTECTIONISM TO ACCESS:
WOMEN'S PARTICIPATION IN CLINICAL TRIALS -
CONFLICT, CONTROVERSY, AND CHANGE

Stacey E. Pauker
April 2002
Class of 2002
Combined Course and Third Year Paper
Professor Peter Barton Hutt

TABLE OF CONTENTS

ABSTRACT	1
INTRODUCTION	1
PART I: Women’s Participation in Clinical Trials: Historical Background	3
A. Protecting Human Subjects: The Evolution of Protectionist Regulation	3
B. Protecting Human Health: The Advent of Inclusionary Regulations	9
C. Current Regulations and Policies: What is the Law Today?	14
PART II: Exclusion v. Inclusion: Arguments For and Against Including Women in Clinical Trials	21
A. Rationales for Including Women of Childbearing Potential in Clinical Trials	22
1. Effect of Exclusion on Women’s Health Care	22
2. Gender-Related Variations in Drug Effects and Response	23
<i>a. Differences Between Men and Women</i>	25
<i>b. Evidence of Gender Differences in Drug-Response</i>	28
<i>c. Impact of Differences on Clinical Trial Design</i>	28
3. Valuable Knowledge Offsets Any Increased Cost	31
4. Respect for Women’s Autonomy and Decision-Making Capacity	33
5. Liability for Exclusion of Women	36
B. Rationales for Excluding Women of Childbearing Potential	37
1. Risk to Potential Children and Legal Liability	38
2. Recruitment and Retention Issues and Increased Cost	40
3. Negative Impact on Women’s Health	42
4. Gender Differences in Drug Response Are Not Significant	42
PART III: Empirical Evidence of Exclusion and Inclusion	44
PART IV: Analysis of Regulations, Policy, and Rationales	49
CONCLUSION	55
APPENDIX	59
SOURCES	65

ABSTRACT

There is a general perception that biomedical research has not given the same attention to the health problems of women that it has given to those of men, and that women may not have benefited from advances in medical diagnosis and therapy because of their lower rates of participation in clinical studies. This paper explores the historical exclusion of women of childbearing potential from clinical trials and the changes in policy and regulations that have occurred. The recent shift from protectionist policies toward policies of access and inclusion remains controversial. Arguments and rationales for and against including women in clinical trials are described, and the empirical evidence of women's participation in these trials is analyzed. It appears that the current regulatory system, supported by federal policy, promotes the inclusion of women in clinical trials, and the results of empirical studies indicate that women are in fact being included. The benefits of inclusion, balanced against the increased cost of including women, reveal that the added cost of inclusion and subgroup differences analysis may jeopardize the long-term goals of improving scientific knowledge and understanding the health problems of all peoples. Alternatives to clinical trials are discussed as a means of producing similar information at lower cost. The paper concludes with a brief discussion of the need to change the popular perception that women are being neglected by clinical research to their detriment, rather than changing the existing policy and regulatory system regarding their inclusion in clinical trials.

INTRODUCTION

In the past two decades, a perception has grown that the nation's clinical research enterprise has focused more on the health problems of men than on those of women, particularly so in regard to clinical trials, and that women have been denied access to advances in medical diagnosis and therapy as a result of being excluded from these trials.¹ At the same time, there have been substantial changes in federal research policies regarding the inclusion of women in clinical trials. The prevailing perception that women have been systematically excluded from clinical research to their detriment is highly controversial, igniting conflict between those who hold the perception and those who do not, and between concerns about protecting women from the risks of participation in research and about their access to its potential benefits.

¹A.C. Mastroianni, R. Faden, and D. Federman, eds., *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1 (Washington, D.C.: National Academy Press, 1994).

This paper explores the participation of women of childbearing potential in clinical trials, the controversy surrounding their participation, and the changes in federal regulations and policies regarding their involvement in an attempt to explain the prevailing perception of exclusion and illuminate the reality of the situation. Most controversial in the area of women's participation in clinical trials is the participation of women of childbearing potential, rather than pregnant women, in drug trials for diseases that affect both men and women, rather than conditions unique to women; the exclusion of pregnant women from trials and the exclusion of women from trials for male-only diseases seems more justified even to the strongest advocates for women's health research.² Thus, this paper focuses on these issues.

Part I describes the historical evolution of current policy and regulations regarding the participation of women of childbearing potential in clinical drug trials. Part II presents the arguments and rationales for and against the inclusion of this subgroup in clinical trials and the analysis of gender differences in drug effectiveness and response. Part III discusses the existing empirical evidence on women's participation in trials. Part IV is an analysis of current policy, regulations, and arguments, and concludes that while current policy and regulations support and promote the inclusion of women in clinical trials, requiring the inclusion of women in all clinical trials may in fact jeopardize, rather than benefit, women's health care due to the expense of subgroup analysis. Alternatives to clinical trials are discussed that can enhance the understanding of women's health at lower cost and without jeopardizing their well-being. The paper concludes with a discussion of how the prevailing perception that clinical research is tilted in favor of men has affected current policy and how women's health care can best be served by changing this perception to reflect the current state of women's participation in clinical trials.

²R.B. Merkatz. 1993. "Women in Clinical Trials: An Introduction," *Food and Drug Law Journal* 48(2): 161-6.

PART I: Women’s Participation in Clinical Trials: Historical Background

Policy development in the area of protection of human research subjects began in 1949 with the issuance of the Nuremberg Code, which outlined standards for the judgment of flagrantly abusive human experimentation conducted by the Nazis during World War II. The Code articulated ten basic principles concerning moral, ethical, and legal requirements of research involving human subjects, including the provision that research subjects must have the legal capacity to give consent, the ability to exercise free power of choice, and sufficient knowledge and comprehension to be able to make an informed decision. The Code also dictated that experiments involving human subjects should yield useful results that cannot be achieved by other methods, avoid unnecessary suffering and injury, assure that risk does not exceed importance, and be done by scientifically qualified persons with adequate facilities for subject protection. The Code further stipulated that human subjects be at liberty to withdraw from the study at any time and that the scientist be prepared to terminate the experiment if continuation was likely to result in injury, disability, or death to the subject.³

A. Protecting Human Subjects: The Evolution of Protectionist Regulation

In response to the Nuremberg Code, the Clinical Center of the National Institutes of Health, a research hospital opened in 1953, formulated guidelines for clinical research. Titled “Group Considerations for Clinical Research Procedures Deviating from Accepted Medical Practice or Involving Universal Hazards,” these guidelines were the first federal guidelines for human studies research and the first official statement requiring committee review of human studies protocols.⁴

During the 1960s and 1970s, several unfortunate events indicated that serious problems remained with re-

³ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1.

⁴ *Id.* at 37.

gard to the protection of human research subjects. Landmark research abuses, including those involving elderly debilitated patients and African-Americans, signaled the need for the clarification and formalization of existing guidelines for human subjects research. In 1963, it was discovered that a physician at the Jewish Chronic Disease Hospital in Brooklyn, New York was experimentally injecting live cancer cells into elderly debilitated patients without proper informed consent.⁵ Review proceedings indicated that the study had not been presented to the hospital's research committee and that several physicians responsible for the patient's care had not been consulted before the injections were given. In 1965, Henry K. Beecher, a Harvard anesthesiologist, gave a highly publicized speech that highlighted cases in the published literature of neglect of the consent process in human subjects research.⁶ Then, in the early 1970s, the abuses of the infamous Tuskegee Syphilis Study were revealed, adding fuel to arguments that human research subjects were not being adequately protected by the existing guidelines and that more formal regulations were needed. This observational study, begun in 1932, involved 400 African-American men many of whom were allowed to remain untreated for the disease even after antibiotic treatment was widely available.⁷ Because the study was initiated before the Nuremberg Code, it had not been subject to any ethical review, and funding for the study had been renewed over the years in accordance with the recommendations of the investigators. Shortly after these abuses were revealed, a congressional panel was convened to review the study's history and to recommend action by the federal government. Included in the panel's final report was the recommendation that the Department of Health, Education, and Welfare's (DHEW) standards regarding informed consent of research subjects be clarified and that an effective enforcement mechanism be devised.⁸ On May 30, 1974, existing guidelines for the protection of human research subjects finally took the shape of federal regula-

⁵*Id.* at 39.

⁶*Id.*

⁷J.H. Jones. *Bad Blood: The Tuskegee Syphilis Experiment* (New York: Free Press, 1981).

⁸U.S. Department of Health, Education, and Welfare (USDHEW). 1973. *Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel*. Washington, D.C.

tions.⁹ Promulgated by DHEW, the regulations established the institutional review board (IRB), a more formal version of the research review committee, as one mechanism for the protection of human research subjects. The responsibilities entrusted to the IRB included the reviewing of risk-benefit ratios, confidentiality protection, informed consent processes, and procedure for selection of subjects to ensure that selection is equitable.¹⁰

In the 1960s and 1970s, as attention focused on the research abuses discovered at the Jewish Chronic Disease Hospital and Tuskegee, health problems caused by the drugs thalidomide and diethylstilbestrol (DES) amplified public sentiment about the need for greater protection for fetuses from risks in science and medicine. These concerns were ultimately translated into protective regulations directed toward women of childbearing potential and pregnant women.

Thalidomide, approved for marketing in 1958 and approved for over-the-counter sale in twenty countries (not including the United States) was used widely, primarily as a sedative and antidote for nausea in early pregnancy.¹¹ Although marketing approval had been delayed in this country, many women received thalidomide from “investigating” doctors who had been given the drug by the manufacturer.¹² As thalidomide was being widely distributed, physicians began to notice a startling increase in the number of children born with a rare set of deformities, the most prominent of which were severe limb malformations. In 1962, when sufficient statistical evidence had been obtained to establish a causal relationship between thalidomide and these deformities, nearly 8,000 children had been affected.¹³ The thalidomide disaster was the result of inadequate research standards, a failure of the drug’s manufacturer to acknowledge early evidence of side effects, and physicians’ uncritical acceptance of promotional claims.¹⁴ Yet, even though the disaster was not in fact the

⁹ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 39.

¹⁰ *Id.*

¹¹ *Id.* at 40.

¹² *Id.*

¹³ G.A. Christie. 1962. “Thalidomide and Congenital Abnormalities.” *Lancet* 2: 249.

¹⁴ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1

result of women's participation in research, the experience nonetheless had a powerful emotional impact that created an aversion to involving pregnant women and women of childbearing age in drug research.¹⁵ The DES experience compounded this aversion.

In the 1940s and 1950s, enthusiastic physicians overlooked large, controlled clinical trials indicating that DES, a synthetic hormone widely prescribed to prevent miscarriages, was ineffective, choosing instead to focus on smaller studies showing that the drug was beneficial.¹⁶ It was not until twenty years later, in the late 1960s and early 1970s, that the side effects of the drug became evident: the daughters of women who had taken DES during pregnancy experienced a rare adenocarcinoma of the vagina.¹⁷ Public trust in science and medicine was shaken once again, particularly because the drug continued to be prescribed even after a controlled study in the 1950s disproved the drug's clinical efficacy, and a protectionist stance toward including fertile women in drug trials was further entrenched.¹⁸ The response from the U.S. science establishment was the creation of new legislation: the Kefauver-Harris amendments of 1962 mandated demonstration that new drugs are effective as well as safe before marketing and included a rigorous preapproval process at the FDA.¹⁹ Again, even though the DES experiences were based on injuries incurred in the context of medical practice rather than research, the substantial costs incurred by pharmaceutical companies through DES-related litigation encouraged the practice of excluding pregnant and pregnable women from clinical research.²⁰

Thus, in 1975, Congress passed the National Research Act which called for the establishment of a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Com-

at 40.

¹⁵L.A. Eckenwiler. 1999. "Pursuing Reform in Clinical Research: Lessons from Women's Experience," *Journal of Law, Medicine, & Ethics* 2(27): 1073-1105.

¹⁶*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 40.

¹⁷*Id.*

¹⁸L.A. Eckenwiler, *supra* note 15 at 1079.

¹⁹C. Levine. 1993. "Women as Research Subjects: New Priorities, New Questions." In: *Emerging Issues in Biomedical Policy: An Annual Review*, Volume 2, R.H. Blank and A.L. Bonnicksen, eds. (New York: Columbia University Press, 1993).

²⁰*Id.*

mission) to identify ethical principles and to develop guidelines for research involving human subjects.²¹ The Commission, which operated between 1974 and 1978, developed guidelines in 1975 for research on fetuses and pregnant women which were incorporated into the Department of Health and Human Service's (DHHS) regulations for research on human subjects. These federal regulations, still in effect today, identify the limited conditions under which an institutional review board (IRB) may approve research on pregnant women and fetuses.²² Subsequent regulations instituted to protect children and prisoners from research abuses have grouped pregnant women in the category of "vulnerable populations," a grouping that has been criticized for implying that pregnant women are incapable of making responsible decisions for themselves and their future offspring.²³

Although DHHD included restrictions on the inclusion of women of childbearing potential in earlier drafts of the regulation concerning pregnant women, these references were eliminated from the final regulation. In 1977, however, the Food and Drug Administration (FDA) issued a guideline for drug development entitled "General Considerations for the Clinical Evaluation of Drugs" recommending that women of childbearing potential be excluded from early phases of drug trials (Phase I and early Phase II) until reproductive toxicity studies were conducted and some evidence of effectiveness had become available, thus formalizing the consensus among clinical researchers in the wake of the DES experience.²⁴ The recommended exclusion was broadly applied to any "premenopausal female capable of becoming pregnant," but explicitly did not apply to women with life-threatening diseases.²⁵ Although the FDA policy explicitly pertained only to the exclusion of women of childbearing potential – defined as such, regardless of whether they were pregnant, sexually active, used contraceptives or intended to conceive – from early phases of drug trials, research in-

²¹National Research Act. July 12, 1974. (Public Law 93-348).

²²*Id.*

²³*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 41.

²⁴Food and Drug Administration (FDA). 1977. *General Considerations for the Clinical Evaluation of Drugs*. (Rockville, MD: FDA).

²⁵*Id.*

investigators and institutional review boards tended to extend the policy to all phases of drug trials.²⁶ This broad interpretation of the FDA guideline was based on concern regarding the well-being of unborn children, the cost and complexity of recruitment (the most convenient cohorts being predominantly male), the fear of legal liability of fetal exposure, and the potentially confounding effects from hormonal changes.²⁷ The 1977 guideline however raised important ethical questions about the appropriateness of assuming that women cannot take steps to avoid becoming pregnant, where necessary, and of deciding for women that protecting the fetus outweighed other possible interests, questions brought to the forefront by the Belmont Report.²⁸

B. Protecting Human Health: The Advent of Inclusionary Regulations

The publication of the National Commission's Belmont Report, outlining the ethical principles expected to govern drug research, was the impetus for the shift away from paternalistic or protectionist policies and toward a greater valuation of the autonomy of research subjects. The Report identified three comprehensive ethical principles that provide an analytical framework for scientists, physicians, research subjects, and reviewers of research proposals to understand the ethical issues inherent in human subjects research. First, individuals should be treated as autonomous agents and persons with diminished autonomy are entitled to protection (respect for persons); second, possible benefits should be maximized and possible harms should be minimized (beneficence); and third, selection of subjects for clinical research should be fair (justice).²⁹

Subsequent interpretations of this report's emphasis on respect for persons raised serious questions about

²⁶ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 41.

²⁷ N.L. Buc. 1993. "Women in Clinical Trials: Concluding Remarks," *Food And Drug Law Journal* 48(2): 223-6.

²⁸ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1978. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, D.C.: Government Printing Office, 1978).

²⁹ *Id.*

the virtual ban on women of childbearing potential participating in early clinical trials.

Further support for reconsidering the policy of excluding women of childbearing potential from clinical trials came from a variety of sources. In the 1980s, AIDS activists working to promote access to experimental AIDS therapies offered the first formal challenge to the protectionist policies of the preceding decades. Frustrated with the length of time required for new drugs to move through the FDA approval process, these activists urged a new mechanism for earlier release of AIDS drugs in the development process.³⁰ In May of 1987, the FDA issued regulations that expanded access to experimental drugs used to treat serious and life-threatening illnesses.³¹ The success of AIDS activists energized the women's health movement.

Observing the success of AIDS activists in reorienting financial and scientific resources to better address AIDS research needs, advocates for women's health began to push for more focused research on health problems unique to women. Women had united around health concerns in the 1970s, exemplified by the publication of *Our Bodies, Ourselves*,³² a women's health care manual created in reaction to a health care system that many women perceived to be unresponsive to their needs, but it was not until the 1980s that women gained sufficient political power to forcefully confront the science and health care bureaucracy. In the late 1980s, when women of the baby boom generation began to reach mid-life and to experience menopause and breast and reproductive cancers, these women became increasingly concerned with the relative lack of attention being paid to women's health in the scientific and medical establishments. Better educated and employed in more powerful positions than their predecessors, baby boom women began to take action by supporting female political candidates, fund-raising for women's issues, and forming interest and advocacy groups to educate themselves and to pressure unresponsive bureaucrats – the same strategies used so successfully by

³⁰D.J. Rothman and H. Edgar. 1990. "New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process," *Milbank Quarterly Supplement* 68(1): 111-142.

³¹*Id.*

³²Boston Women's Health Book Collective. 1973. *Our Bodies, Ourselves*. New York: Simon & Schuster (1973).

AIDS activists. In addition, dramatic increases in medical school enrollment among women in the 1970s began to produce a vocal group of medical professionals who questioned current priorities and policies in women's health research.³³

In 1985, the U.S. Public Health Service Task Force on Women's Health Issues reported that the "historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the health care they receive."³⁴ The recommendations accompanying the report provoked NIH in 1986 to formulate a new policy that encouraged – but did not mandate – inclusion of female subjects in all clinical research done by funding recipients.³⁵ The policy also stated that funding applicants should provide clear rationales for proposed exclusions of women and that investigators should evaluate gender differences in their findings. In 1988, the FDA also published a guidance entitled "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," emphasizing the importance of including analyses of demographic data in new drug applications (NDA).³⁶

However, NIH failed to publish implementation guidelines for its policy until 1989, and in 1990, the General Accounting Office (GAO) released a report outlining the ineffectiveness of the NIH policy, and focusing even more public attention on the issues of women's inclusion in clinical research and the implications of this inclusion for the status of women's health. In testimony delivered to the House of Representatives, a GAO representative stated that the unautomated, decentralized recordkeeping had prevented GAO from systematically evaluating the effectiveness of the NIH policy and that NIH had no way to measure the policy's impact on the research it funds. GAO also reported that the 1986 policy had not been well-disseminated internally

³³ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 42.

³⁴ U.S. Public Health Service (USPHS). 1985. "Report of the Public Health Service Task Force on Women's Health Issues," *Public Health Reports* 100(1): 73-106.

³⁵ General Accounting Office (GAO). 1990. Summary of Testimony by Mark V. Nadel on Problems in Implementing the National Institutes of Health Policy on Women in Study Populations. Given before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, House of Representatives, 18 June 1990. (Washington, D.C.: GAO).

³⁶ Food and Drug Administration (FDA). 1988. *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications*. (Rockville, MD: FDA).

to individual institutes or centers, nor to prospective grant applicants and therefore these policies had not been implemented consistently, if at all. Different institutes at NIH also varied in their interpretation of the policy, adding to its inconsistent application. In addition, the GAO report highlighted some of the larger, more expensive NIH-funded clinical studies that had included only men as evidence of the ineffectiveness of the policy, such as the Physician's Health Study, an all-male study of the role of aspirin in the prevention of heart attacks, and all-male studies of the relationships between caffeine and heart diseases, and cholesterol levels and heart disease.³⁷

After the release of the 1990 GAO report, women's health advocacy groups and other organizations initiated their own efforts to clarify the picture of women's participation in clinical research. Popular opinion which once supported protective policies began to shift toward labeling these policies paternalistic and discriminatory. The rationales behind clinical studies that had proceeded without question began to be challenged with questions such as "How could the NIH-sponsored Multiple Risk-Factor Intervention Trials of heart disease exclude women when women as well as men were dying from heart disease?"³⁸ and "How could the Baltimore Longitudinal Study of Aging include no women when the elderly population in this country is disproportionately female?"³⁹ In response to the impact of the GAO report, NIH created the Office of Research on Women's Health (ORWH), and gave it a three-part mandate:

1. to strengthen and enhance research related to diseases, disorders, and conditions that affect women and to ensure that research conducted and supported by NIH adequately addresses issues regarding women's health;
2. to ensure that women are appropriately represented in biomedical and behavioral research studies supported by NIH; and
3. to foster the increased enrollment of women in biomedical research especially in pivotal decisionmaking roles within both clinical medicine and the research environment.⁴⁰

³⁷GAO, 1990, *supra* note 35.

³⁸Multiple Risk-Factor Intervention Trial Group, Statistical Design Considerations in the NHLI Multiple Risk Factor Intervention Trial (MRFIT). 1977. *Journal of Chronic Diseases* 30:261-275.

³⁹*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 44.

In 1991, NIH also promulgated a strengthened policy to govern the awarding of federal research grants in the form of instructions to grant applicants to ensure that women and racial and ethnic groups be included. For extramural clinical research projects (those carried out by research institutions throughout the U.S. and the world) “[a]pplications for grants and cooperative agreements that involve human subjects are required to include minorities and both genders in study populations so that the research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study.”⁴¹ The applicant must describe the proposed study population composition and provide a “compelling” justification for gender or racial and ethnic group exclusion. The investigator must also address gender and racial and ethnic issues in “developing a research design and sample size appropriate for scientific objectives of the study.”⁴² Although what constitutes a “compelling” reason for exclusion is not defined, the explanatory memorandum to NIH staff and peer advisory groups accompanying the policy directs them to consider sufficient only “strong scientific or practical reasons for the exclusion of women or racial and ethnic groups from clinical research.”⁴³ Some of the potentially acceptable justifications listed include research on a predominantly or exclusively male condition, research that presents an unacceptable risk for women of childbearing age, certain pilot and feasibility studies in which gender differences may not be germane, research in an area that has already been extensively studied in women, and, in certain instances, studies that would be prohibitively expensive.⁴⁴ Intramural research projects (operated by federal employees on NIH campuses) were subject to a less restrictive policy, requiring only that gender-based exclusions be indicated and a clear rationale be provided. Finally, NIH devised a plan to facilitate the implementation of the new policy, including educational programs for

⁴¹National Institutes of Health and Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). 1990. “NIH/ADAMHA Policy Concerning Inclusion of Women in Study Populations.” *NIH Guide* 19(31): 18-19.

⁴²*Id.*

⁴³*Id.*

⁴⁴National Institutes of Health (NIH). 1990. “NIH Instruction and Information Memorandum OER 90-5.” December 11.

reviewers, investigators, and NIH staff, and for a coding system to track gender and racial and ethnic group representation in clinical studies.⁴⁵

The GAO issued a second report in 1992 addressing the inclusion of women in clinical trials, and examining the FDA's policies and the pharmaceutical industry's practices regarding experimental drug testing in women.⁴⁶ The report stated that although women were included in most of the drug studies reported by pharmaceutical companies that had secured FDA approval for a new drug between January 1988 and June 1991, for more than sixty percent of the drugs, the representation of women in the test population was less than the representation of women in the population with the corresponding disease. Representation of women was found to be particularly poor in cardiovascular drug trials, a finding about which the GAO was especially concerned because this is an area in which gender differences in drug response had been observed. In addition, GAO indicated that pharmaceutical manufacturers frequently failed to analyze trial data for gender differences.⁴⁷

C. Current Regulations and Policies: What is the Law Today?

Finally, on June 10, 1993, the NIH Revitalization Act, which grew out of the Women's Health Equity Act introduced in 1990 and calling for among other things the inclusion of women and racial and ethnic groups in NIH-sponsored or funded clinical research, was signed into law by President Clinton.⁴⁸ The Act requires

⁴⁵ADAMHA, 1990, *supra* note 41.

⁴⁶General Accounting Office (GAO). 1992. "Women's Health: FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing." GAO/HRD-93-17. Washington, D.C.: GAO.

⁴⁷*Id.*

⁴⁸NIH Revitalization Act of 1993 (Public Law 103-43). Reintroduced in 1991, the Women's Health Equity Act (WHEA) contained 22 bills that addressed research, care, and prevention issues in women's health. During the 1991-1992 legislative year, six of the research-related provisions of the WHEA (including the provision to permanently authorize the ORWH) were incorporated into the NIH Revitalization Act. These provisions authorized additional funding for breast cancer, ovarian and other reproductive cancers, and osteoporosis and other bone disorders; they also called for the establishment of three

that women and racial and ethnic groups be included as subjects in each intramural and extramural clinical research project supported by NIH. It further requires that any NIH-funded clinical trial that includes women and racial and ethnic minorities as participants be designed and carried out so as to provide for valid analysis of whether the variables being studied affect these subpopulations differently from other participants in the trial. Cost may be considered only when the data regarding women or members of minority groups that would be obtained in the project have been or will be obtained through other means that offer comparable quality; otherwise, cost is not an appropriate reason for excluding women. The inclusion of women and minorities may not be required if substantial scientific data demonstrate that there is no significant difference between the effects of the intervention or variables under study on these groups and the effects on the subjects included in the trial. Furthermore, NIH is instructed to conduct or support outreach programs for recruitment and retention of women and racial and ethnic group participants in clinical research projects. The law, however, does allow for exemption in cases of research that are inappropriate with respect to the health of the subjects, the purpose of the research, or other circumstances determined by NIH.⁴⁹

On July 22, 1993, the FDA released a new guideline, “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” lifting the 1977 guideline recommending the exclusion of women of childbearing potential from early clinical trials, including pharmacology studies and early therapeutic studies.⁵⁰ The introduction to this guideline indicates that the broad principles that are outlined for the inclusion of women in the early phases of clinical trials will also be applied to FDA approval processes for biological products and medical devices. The guideline explains that subjects in a given clinical study should reflect the population that will receive the drug when it is marketed, and suggests that patients of both contraceptive research centers and two fertility research centers. One of the provisions included a policy regarding inclusion of women and racial and ethnic groups in NIH-sponsored or -funded clinical research.

⁴⁹ *Id.*

⁵⁰ Food and Drug Administration (FDA). 1993. “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” Notice, *Federal Register* 59(139): 39406-39416.

genders be included in the same trial to permit direct comparison of genders within the studies. The guideline also explicitly discredits routine exclusion of women from bioequivalence trials because changes during the menstrual cycle may cause intrasubject variability. Inclusion of women in these studies is expected to indicate if there is a possible need for concern about the variations in response to a drug based on the hormonal variations of the menstrual cycle. The guideline outlines the FDA's expectations for the data analyses of gender differences and other subgroup differences, and expects these analyses to be performed and explained in an application for approval of a new drug. The guideline emphasizes the importance of pharmacokinetic (the effect of the body on the drug) studies to define gender-related differences in drug responses, but does not expect pharmacodynamic (the effect of the drug on the body) and effectiveness studies to be conducted separately on men and women unless the analyses by gender of clinical trials and pharmacokinetic studies indicate significantly different gender-related response. Finally, the guideline reiterates the FDA's belief that large-scale exposure of women of childbearing potential should not take place until after the results of animal toxicity tests are analyzed, and recommends that clinical protocols include provisions for the use of contraception or abstinence for the entire time a subject will be exposed to the drug. In the clinical evaluation of drugs that carry the risk of causing abnormalities in reproductive organs or their function (as identified in animals), the risks of exposing individuals of reproductive potential must be weighed against the potential benefits of the drug.⁵¹

More recently, the Food and Drug Administration Modernization Act of 1997 amended Section 505(b)(1) 21 U.S.C. 355 (b)(1) by adding "The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials..."⁵² This Act mandates neither the

⁵¹*Id.*

⁵²Food and Drug Administration Modernization Act. 1997. Sec. 115 Clinical Investigations. (b) Women and Minorities.

inclusion nor the exclusion of women from clinical trials. The Center for Drug Evaluation and Research (CDER) was assigned the responsibility for reviewing and implementing this section of the FDAMA for the FDA, and to accomplish that task established the FDAMA Women and Minorities Working Group with representation from the FDA and the National Institutes of Health.⁵³

In 1998, the Working Group concluded that additional guidance on the inclusion of women in clinical trials was not needed.⁵⁴ In coming to this conclusion, the Group reviewed and evaluated existing guidance regarding the inclusion of women and minorities in clinical trials, specifically, the 1988 “Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications,”⁵⁵ the 1993 “Guideline for the Study and Evaluation of Gender Differences in Clinical Evaluations of Drugs,”⁵⁶ the 1998 regulation “Final Rule: Investigational New Drug Applications and New Drug Applications,”⁵⁷ and the 1998 proposed clinical hold rule “Investigational New Drug Applications; Proposed Amendment to Clinical Hold Regulations for Products intended for Life-Threatening Diseases.”⁵⁸ The Group found that taken together these guidelines and regulations, which are still in effect, provide sufficient guidance concerning the inclusion of women and minorities in clinical research and ensure that women are included appropriately in clinical trials and that data is analyzed to ensure that gender information is available and understood.⁵⁹ The 1988 guideline emphasizes the importance of including analyses of demographic data in NDA applications. The 1998 regulation requires that analyses of effectiveness and safety data for important demographic subgroups, including gender and racial subgroups, be submitted in NDAs and that enrollment of subjects into clinical studies for drug and biological products be tabulated by important demographic subgroups (age group, gen-

Rockville, MD: FDA.

⁵³ *FDAMA Women and Minorities Working Group Report*, July 20, 1998 (visited February 2002) <<http://www.fda.gov>>.

⁵⁴ *Id.*

⁵⁵ FDA, 1988, *supra* note 36.

⁵⁶ FDA, 1993, *supra* note 50.

⁵⁷ 21 CFR Parts 312 and 314, February 11, 1998.

⁵⁸ 21 CFR Part 312, *infra* note 61.

⁵⁹ *FDAMA Women and Minorities Working Group Report*, *supra* note 53.

der, and race) in investigational new drug (IND) annual reports. This final rule allows the FDA to refuse to file any NDA that does not analyze safety and efficacy information appropriately by gender. The critical importance of including all appropriate subsets of the population in product development, according to the Group, is clearly articulated in the 1993 guideline, which states:

In general, drugs should be studied prior to approval in subjects representing a full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave qualitatively similarly in demographic (age, gender, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many qualitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse effect. Recognition of these differences can allow safer and more effective use of drugs. Rarely, there may be qualitative differences as well. It is very difficult to evaluate subsets of the overall population as thoroughly as the entire population, but sponsors are expected to include a full range of patients in their studies, carry out appropriate analyses to evaluate potential subset differences in the patients they have studied, study possible pharmacokinetic differences in patient subsets, and carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, are suggested by existing data, or that would be particularly important if present.⁶⁰

Finally, the 1998 proposed clinical hold rule (the final rule was published in June of 2000) expands upon this guidance by allowing the FDA to place a clinical hold on one or more studies under an IND if a sponsor proposes to exclude men or women with reproductive potential from participation in an investigation only because of risk or potential risk of reproductive or developmental toxicity from the use of an investigational drug product.⁶¹ The Group believed that any lingering exclusionary policies would be addressed by the finalization of the 1998 proposed rule.

In summary then, a variety of policies and regulations currently exist concerning the inclusion of women in clinical trials. How these various policies and regulations fit together is somewhat complex. NIH, located within the Public Health Service of the Department of Health and Human Services, is the single largest supporter of biomedical and behavioral research (health R&D) and development in the world.⁶² NIH un-

⁶¹21 CFR Part 312, June 1, 2000, *Final Rule: Investigational New Drug Applications; Amendment to Clinical Hold Regulations for Products intended for Life-Threatening Diseases*.

⁶²*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1

derwrites approximately 73 percent of all health R&D supported by the U.S. federal government.⁶³ Thus, research sponsored, funded, or conducted by the NIH is subject to the NIH Revitalization Act of 1993 which requires the inclusion of women in NIH-sponsored or funded clinical trials and the analysis of subgroup differences. The FDA, also a Public Health Service agency, functions under the Food Drug, and Cosmetic Act (FDCA) which gives the commissioner of the FDA the authority and responsibility to regulate the testing and marketing of drugs, biologics, and medical devices.⁶⁴ The FDAMA of 1997, which governs the FDA, does not require the inclusion of women in clinical trials. Although the 1993 FDA guideline encourages the inclusion of women and the analysis of gender differences, these guidelines do not have the force of law or regulation which guide the FDA, are not binding on the FDA, and do not create or confer any rights, privileges, or benefits for or on any person. These guidelines are provided as an aid to organizations involved in the evaluation of new drugs for FDA approval who wish to market such drugs. The guideline does not mandate the inclusion of women of childbearing potential, or women in general, relying instead on the “interplay of ethical, social, medical, legal, and political forces” to encourage greater participation of women in the earlier stages of clinical trials.⁶⁵ Institutions that conduct clinical trials and research funded by NIH involving drugs, biologics, or medical devices are subject to all applicable policies and regulations of both NIH and FDA.

Currently, this means that, according to the NIH Revitalization Act, funding can be denied if women are excluded from clinical trials, according to FDA’s 1993 guideline, women should be included in clinical trials, according to the FDAMA, women are not required to be included in clinical trials, and according to the 2000 clinical hold rule, the FDA can place a clinical hold on studies under an IND that have excluded men

at 129.

⁶³ *Id.*

⁶⁴ *Id.* at 131.

⁶⁵ FDA, 1993, *supra* note 50.

or women, but does not require this action. Thus, the bottom line is that, funding aside, current law does not require the FDA to include women in clinical drug trials. Although the NIH funds most of these trials and requires women to be included, the FDA itself is governed by no such regulation. Therefore, the FDA can, in theory even if not in practice, exclude women, despite the fact that the 1993 guideline encourages the inclusion of women in clinical trials, thereby reflecting a policy position different from the FDA's regulatory position.

PART II: Exclusion v. Inclusion: Arguments For and Against Including Women in Clinical Trials

The historical evolution of federal policies regarding women's participation in clinical studies over the past several decades arises from the conflict between two public policy positions: protectionism and access.⁶⁶ Emphasis on the need to protect research subjects burgeoned in the 1950's and 1960s in response to revelations of abuses of the research process. This emphasis was reinforced by the discovery of adverse outcomes in the children of women who had taken certain drugs during pregnancy. The legislation passed in the mid-1970s was designed to protect research subjects from unethical treatment. The regulations and guidelines stemming from this legislation also were designed to protect against fetal injury in their restrictions on the inclusion of pregnant women and women of childbearing potential in drug trials. In later years, however, these guidelines and regulations put in place to protect research subjects were challenged by claims that they were overprotective and overly exclusive, and therefore detrimental to the health of the very persons they were intended to protect. As a result, new guidelines and regulations emerged to promote increased access to health care and greater patient autonomy. This change in policy, however, remains controversial.

While most health care advocates, researchers, and academics in the field would agree that women's health is a serious issue deserving attention, these same individuals continue to disagree about whether this attention should manifest itself in the form of including women in clinical trials. There exist a variety of rationales and arguments both for and against the inclusion of women of childbearing potential in clinical trials, all of which must be considered before one can form an opinion on the subject.

A. Rationales for Including Women of Childbearing Potential in Clinical Trials

⁶⁶J. A. Sechzer, V.C. Rabinowitz, F.L. Denmark, M.F. McGinn, B.M. Weeks, C.L. Wilkens. 1994. "Sex and Gender Bias in Animal Research and in Clinical Studies of Cancer, Cardiovascular Disease, and Depression." In: *Forging a Women's Health Research Agenda: Policy Issues for the 1990s*. A. Sechzer, A. Griffin, and S.M. Pfafflin, eds., (New York, New York: New York Academy of Sciences, 1994).

Rationales for including women of childbearing potential in clinical trials by lifting the 1977 guideline favoring their exclusion include the detrimental effect that exclusion has on women's health in general, the identification of gender-related variations in drug effects and response, the valuable knowledge that results from the inclusion of women which offsets any increased cost of inclusion, respect for women's autonomy and decision-making capacity in reproductive issues, and the potential for liability that may result if women are excluded from clinical trials.

1. Effect of Exclusion on Women's Health Care

When women are excluded from clinical trials, the development of clinical data relevant to women's health is inhibited. More importantly, the risk to women's health increases. If women were excluded from clinical trials, after FDA standards for drug approval and drug marketing are met, pharmaceuticals that were never tested on women would be used by women, and in some cases women would be the primary users, despite the fact that there would be no clinical basis for predicting the effects of such drugs in women. Not only would side-effects occur in a certain percentage of women who took these drugs, but those side-effects would involve many more women because the population exposed to potential side-effects would be much larger during mass consumer marketing than during clinical trials. Furthermore, when interventions are not adequately studied in women, women's medical care may be seriously compromised; physicians may choose not to give female patients available treatments, or the treatments physicians give these patients may pose greater risks to women than to men. Literature in the field indicates "residual exclusion" of women from access to medications tested only in men;⁶⁷ physicians are reluctant to use drugs in populations for which safety

⁶⁷H. Minkoff, J.D. Moreno, and K.R. Powderly. 1992. "Fetal Protection and Women's Access to Clinical Trials," *Journal of*

has not been demonstrated during clinical trials. Other research indicates that women may be diagnosed later or receive less aggressive treatment than men for specific conditions, most notably studies concerning patients with kidney disease gaining access to dialysis and transplantation, the diagnosis of lung cancer by sputum cytology, and the diagnosis of heart disease. Several studies find that women with heart disease may be diagnosed later than men and that women are less likely than men to have invasive procedures such as coronary angioplasty or coronary artery bypass surgery. Finally, lower case survival rates have been observed in women following myocardial infarction and diagnosis of AIDS, reflecting later diagnosis and less aggressive treatment.⁶⁸ Excluding women from clinical studies thus appears to result in information deficits regarding how women respond to drugs and the causes of morbidity and mortality in women, deficits with severe consequences for women's health.

2. Gender-Related Variations in Drug Effects and Response

Implicit in the 1993 guideline reversing the 1977 guideline and in the policy of inclusion mandated by the NIH Revitalization Act of 1993 is the underlying assumption that there are meaningful differences between the sexes and that the results of male-only studies cannot be reliably or safely generalized to women. If men and women responded identically to therapy, the issue of representation of women in clinical trials would be less important. Indeed, there is a general belief among researchers that, in most situations, women and men will *not* differ significantly in their responses to treatment.⁶⁹ Even for diseases where men and women differ significantly in the likely time of onset, such as heart disease, most clinical researchers would argue that men and women respond in much the same way to treatment and experience a similar evolution of the disease. The reasons for this belief are rooted in several observations regarding health problems relevant to both men

Women's Health 1:137-140.

⁶⁸C.S. Weisman and S.D. Cassard. 1994. "Health Consequences of Exclusion or Underrepresentation of Women in Clinical Studies (I). In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

⁶⁹*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 84.

and women: for the majority of drug treatments, efficacy and safety do not depend on such factors as body mass, adipose tissue, hormones, or other factors associated with gender; treatments by surgical procedure for diseases associated with both genders seldom differ because the patient is female rather than male, and to the extent that women may be treated differently, it is because of factors associated with gender but not specific to gender, such as bone mass and organ size; and a long history of nonhuman research supports the conclusion that subgroup differences are rare.⁷⁰

Nevertheless, there is concern in the field that clinicians may be too quick to assume that there are no differences between men and women, rather than testing for gender-related effects.⁷¹ Although significant gender differences in drug response have not been detected in the majority of cases, when they are detected, these differences can be highly significant in terms of diagnosis and treatment, thus emphasizing the need for clinical investigators to ascertain under what conditions such gender differences are likely to occur and to design clinical studies accordingly. In other words, where gender differences are evident, the results of medical research conducted on men cannot be generalized to women without sufficient evidence, via inclusion of women in clinical trials, that the results in fact apply to women.

a. Differences Between Men and Women

For the purposes of health research, there are many meaningful differences between the sexes which have implications for how clinical trials should be carried out, particularly in terms of including women in these trials. These differences by gender include differences in body size, composition, and metabolism, differences in aging, behavioral and psychosocial differences, and hormonal differences. On average, women are smaller

⁷⁰*Id.*

⁷¹*Id.* at 85.

than men in weight, height and surface area; this may affect drug dosing, which may be more accurately based on body weight or surface area than on a fixed dose, as most adult dosing is done. If a drug is administered on the basis of body weight or surface area, the average adult male will receive a larger dose than the average adult female. If weight or surface area are not taken into consideration however, and men and women are given the same dose, then the average male will in fact receive a smaller dose per pound of body weight or per inch of surface area than the average female. If the drug has minimal toxicity or a wide therapeutic index,⁷² these differences in dosage may be of little consequence, but if the therapeutic index is narrow or the toxicity severe, these differences may be of critical importance. Compared with men, women also have a lower ratio of lean body mass to fatty tissue, a difference that may affect drug disposition because the water content and metabolism of fatty tissue and muscle tissue differ. Lipid-soluble drugs have a greater volume of distribution in women, thereby affecting the appropriate therapeutic dose. The metabolism of men, at all ages after sexual maturation, is also higher than that of women. Drug metabolism differences by gender are not well-understood but are clearly demonstrated by drugs such as nicotine, aspirin, and some anticoagulants. Men and women also differ in the presence and concentration of hormones within the body, such as estrogen, progesterone, prolactin and testosterone, and in their concentrations of serum iron, uric acid, creatinine phosphokinase, and gamma glutamyl transpeptidase. Hormonal differences may alter the pharmacokinetics and pharmacodynamics of certain drugs while differences in other element concentrations are important in distinguishing the normal from the abnormal in selected disease states.⁷³

Women live longer than men by an average of seven years and presently constitute fifty-nine percent of those over age sixty-five and nearly seventy-five percent of those over age eighty-five. While many of the medically

⁷²Therapeutic index refers to the doses, blood concentration, or receptor concentration necessary to achieve a positive therapeutic response versus those amounts that elicit a toxic response.

⁷³*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 86-88.

and scientifically relevant differences that exist between younger men and women persist into old age, men and women over age sixty-five also experience gender-related health problems that are unique to their age group. Women over sixty-five suffer more adverse events related to medication than do men in the same age group. Although older men and women both experience decreases in lean body mass and increases in fat tissue as a fraction of body weight, these changes are more pronounced in women, such that certain drugs may have a more immediate toxic effect or a more prolonged effect in older women than in older men. Men and women over sixty-five also differ with respect to the diseases and conditions that commonly affect them. Older women are affected by rheumatoid arthritis three times more frequently than men, and osteoporosis, digestive disorders, and thyroid diseases are far more common in women than men. Mental health problems, such as depression, anxiety disorders, sleep disorders, mania, and late-onset psychosis also afflict older women to a greater extent than older men, and neurodegenerative diseases such as Alzheimer's disease and certain movement disorders affect women disproportionately.⁷⁴

Men and women further differ in several psychosocial variables, most of which pertain to gender roles and lifestyle, that can affect disease risk and treatment. There are stresses associated with the multiple roles women typically assume in taking on the responsibilities of balancing work and family that many men never experience. Women also are more likely to be the victims of domestic violence leading to physical and psychological injuries. Lifestyle differences between men and women include the fact that women tend to exercise less regularly than men and that women drink less alcohol and smoke tobacco less than men. Cultural emphasis on thinness and beauty in women translate into a higher prevalence of eating disorders and high use of over-the-counter diet pills as compared with men.⁷⁵

In addition to the ways in which men and women differ as a matter of degree, men and women also differ

⁷⁴*Id.* at 89-90.

⁷⁵*Id.* at 90-91.

in ways specific to one gender. Between menarche and menopause, women experience the menstrual cycle characterized by fluctuating levels of the hormones estrogen and progesterone. These hormonal changes can affect drug disposition such that females may benefit from variable drug dosing tailored to their menstrual cycles. Hormones may also affect the success of some surgical treatments. Menopause is also unique to women and the characteristic end in the production of estrogen, as well as the fact that many women engage in estrogen replacement therapy to reduce or eliminate the unpleasant symptoms associated with menopause, can affect women's risk of certain diseases.⁷⁶

In sum, all of these differences between men and women have important consequences for clinical trials. Differences in size, fat ratios, and metabolic rates are associated with differences in drug concentration, metabolism, and response. Psychosocial differences are associated with differences in risk factors and in adherence to experimental protocols. These differences can further change over time, both in the short term – during the menstrual cycle – and long term – with aging. Advocates for inclusion argue that women must be included in clinical trials because of these significant differences between men and women.

b. Evidence of Gender Differences in Drug-Response

Several studies have shown that existing gender differences do in fact affect drug response. After a heart attack, the response of women to agents for combating thrombosis is unequal.⁷⁷ Women show less benefit than men from oral anticoagulants and thrombolytic agents with respect to reduced mortality.⁷⁸ Women also have more bleeding episodes with thrombolytic agents.⁷⁹ This is especially significant because women are twice as likely as men to have a second heart attack within a year of the first. Their lesser therapeutic response may explain why women are twice as likely as men to die within the first few weeks after a first myocardial infarction, and emphasizes the need for heart attack treatments to be tested on women. Women's

⁷⁶*Id.* at 91.

⁷⁷W.M. Davis. 1998. "Impact of Gender on Drug Responses," *Drug Topics*, October 5, 1998.

⁷⁸*Id.*

⁷⁹*Id.*

response to antihypertensive drugs also differs from that of men, and young and middle-aged women are found to suffer more adverse effects from hypertension therapy than men.⁸⁰ Women have been found to take twice as long as men to wake up from anesthesia and the class of painkillers called kappa opioids seem to work twice as well for women as for men.⁸¹ The fact that women respond differently to so many treatments supports their inclusion in clinical drug trials.

c. Impact of Differences on Clinical Trial Design

Because men and women differ in these ways, clinical drug trials must be designed to take into account gender-related variations in drug effects and response. This design, women's health advocates argue, not only fosters inclusion of women in clinical trials but also serves to promote scientific validity. Methodological implications of gender equity in clinical trials include concerns about external and internal validity, homogeneity versus heterogeneity, and subgroup analysis of interaction effects. When women are excluded from clinical trials, external validity – the ability to generalize the findings obtained from a sample to a broader population – is jeopardized since women clearly exist in the population but are not represented in the sample.⁸² It should be mentioned that in practice, external validity in any clinical trial is an oxymoron. External validity is based on drawing a representative sample of the population of interest. Clinical trials, however, do not take a random sample from a representative population; rather, the members of a study cohort differ from the population about which inferences are to be made in several important ways. Study participants are volunteers. These volunteers are screened to see if they meet selection criteria, and then randomized into treatment and nontreatment groups. The inclusion and exclusion criteria produce a more narrowly defined set of subjects than the group that may be eligible for treatment. To minimize the number of subjects

⁸⁰J.L. Willis. 1997. FDA Consumer Special Report. "Equality in Clinical Trials: Drugs and Gender." In: *Your Guide to Women's Health*, Third Edition, Office of Special Health Issues (placed on the web Dec. 24, 1997) (visited February 2002) <<http://www.fda.gov>>.

⁸¹*Id.*

⁸²R.B. Merkatz, R. Temple, S. Sobel, K. Feiden, D.A. Kessler, et al.. 1993. "Women in Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy," *New England Journal of Medicine* 329 (4): 292-6.

who drop out for instance, clinical trials often exclude people who plan to change residence during the follow-up period, people likely to die soon from a disease other than the one being investigated, and people the investigators believe will not follow the requirements of the protocol.⁸³ Thus, achieving true external validity is practically impossible. However, despite the fact that clinical trials cannot truly speak to external validity, this design can achieve internal validity – how consistently and how well the treatment works.⁸⁴ Clinical trials can illuminate gender differences in treatment effects, and in that sense can contribute to the knowledge and understanding of how women and men differ in their responses to treatment. When a response to a treatment cannot be generalized from the sample to the population as a whole, it is essential that enough members of the relevant subgroups be included in the sample so that a differential response can be detected and measured. Including women in clinical trials means that even if a study has no external validity, the study will have value due to its internal validity.

In order to assess the effect of treatment, clinical trials in general must balance conflicting desires for homogeneity and heterogeneity.⁸⁵ Ideally, the study cohort is homogenous enough to yield a high probability of learning whether a therapy is safe and effective but heterogeneous enough to ensure that the observed results are not applicable only to a narrowly defined subgroup. Clinical investigators try to reduce or eliminate sources of variance that are under their control in order to isolate the effects of the drug on study participants from effects due to differences among the study participants; to do this, investigators construct criteria for the selection of subjects that are intended to reduce variance by recruiting the most homogenous sample possible. The smaller the anticipated sample size of the trial the more important it is to recruit a homogenous sample with regard to factors known to affect treatment. Variations in the population enrolled in a small trial can have a greater effect on the results than in a large trial because randomization into

⁸³*Id.*

⁸⁴*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 97.

⁸⁵J. C. Bennett. 1993. “Caring For Women’s Health – What is the Problem? ,” *New England Journal of Medicine* 329 (4): 288-91.

treatment groups is more likely to serve its purpose in a large trial than in a small one. In addition, the ability to adjust for differences in the composition of the study groups through regression techniques is limited if not completely precluded in a small trial while it is the method of choice for adjustment in large trials. However, at the same time that investigators seek a homogenous sample, in some situations a homogenous response cannot be assumed for specific subgroups of the population. Where this is true, it is essential that the sample be sufficiently heterogeneous by including enough members of the relevant subgroups in the sample to ensure that the results are applicable to those not included in the sample. Exclusion of a given subgroup from a study precludes formal inferences about the expected results for that subgroup. In the case of women, the previous discussion indicates that the existing differences between men and women make it impossible to assume a homogenous response when women are excluded and thus precludes formal inferences from a male-only sample to the population as a whole.

While all investigators must balance the benefits of using homogenous samples – isolating drug effects – with the importance of including subgroups such as women – making their research meaningful beyond the study itself, advocates for inclusion argue that the known differences between men and women and the effect of these differences on drug response clearly support the inclusion of women in clinical drug trials and outweigh investigators' desire for homogeneity in their samples. Taking into account the myriad differences between men and women and the importance of being able to generalize study results from the study sample to the population, investigators need to include women in their research if they hope to generalize their results to this subgroup.

3. Valuable Knowledge Offsets Any Increased Cost

Including women in clinical trials is also supported by the fact that the cost and efficiency gains that investigators' use to justify excluding women may not be valid and, if valid, are offset by the gains in knowledge that result when women are included. In the 1970s, women were excluded from two large preventative clinical trials, as previously discussed – the Physicians' Health Study and the Multiple Risk Factor Intervention Trial (MRFIT). The primary reason for excluding women from the Physicians' Health Study was the gender mix of the physician cohort approached for study, ninety percent of which was male.⁸⁶ The number of women in the cohort was not large enough for a gender-by-treatment interaction analysis. Despite the fact that the investigators' reservations about their ability to perform such an analysis were valid, enrollment of a specified subgroup does not obligate them to perform interactive analysis for that subgroup, nor does the analysis need to be definitive if performed. Even without this analysis, the sign and size of any difference observed for women, had they been included, would have provided some general indication of whether the result obtained in men is consistent with that observed in, and thus generalizable to, women. Women may also have been excluded from clinical trials for reasons of efficiency. If the increase in information gained was not proportionate to the increased costs of including women, perhaps it was rational to exclude women. For example, if including women would have resulted in a ten percent increase in person-years of follow-up information, then to justify excluding women it would be necessary to show that including them would have increased costs by more than ten percent.⁸⁷ In the case of the Physicians' Health Study, including women would likely have added valuable follow-up information without adding disproportionate costs since the costs for screening, treatment, and follow-up of each participant were relatively low. The exclusion of women from MRFIT was also based on scientific and efficiency grounds. Screening costs were high because it was necessary to find people with a defined risk profile based on smoking behavior, cholesterol level, and blood pressure, assessments which required the collection and analysis of blood and blood pressure and

⁸⁶ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 99.

⁸⁷ *Id.*

individual interviews.⁸⁸ Nearly 362,000 men were screened to produce the 12,866 men enrolled in the trial; had women been included, the cost of the trial would have been substantially higher. Nonetheless, those in favor of including women in clinical trials argue that including women in trials like these produces valuable information which offsets the increased cost.

4. Respect for Women's Autonomy and Decision-Making Capacity

From an ethical perspective, the exclusion of women of childbearing potential from clinical trials implies a lack of respect for their autonomy and decision-making capacity concerning reproductive issues. The ethical principles articulated in the Belmont Report – respect for persons, beneficence, and justice – as well as recent Supreme Court decisions suggest that women should have the right to make their own risk-benefit choices about their potential pregnancies and their participation in clinical trials.⁸⁹ The Belmont Report's acknowledgement that individuals should be treated as autonomous agents and only those persons with diminished autonomy should be protected promotes a woman's right to choose whether or not to participate in a clinical trial, rather than to be excluded in a paternalistic effort to protect her well-being. The Pregnancy Discrimination Act,⁹⁰ as interpreted by the Supreme Court in the landmark case of *United Automobile Workers v. Johnson Controls*,⁹¹ prohibits the blanket exclusion of pregnant women from jobs they are qualified to perform solely because working conditions pose potential risks to exposed

⁸⁸ *Id.*

⁸⁹ T.D. Keville. 1994. "The Invisible Women: Gender Bias in Medical Research" *Women's Rights Law Reporter* Volume 15, Numbers 2&3, Winter 1993/Spring 1994.

⁹⁰ 42 U.S.C. Sec. 2000e(k).

⁹¹ 111 S.Ct. 1196, 1991.

fetuses. Although the purposes of clinical trials are manifestly different from the purposes of employment, the Court's emphasis in *Johnson Controls* on a woman's right to participate in decisions about fetal risk underscores the principle of autonomy and further promotes allowing women the right to choose whether to participate.

Assessing the potential risks and benefits of clinical research is not an easy task, nor is it a process that enjoys mathematical precision. People disagree in their evaluations of the magnitude of risks and benefits and how to weigh risks against potential benefits, and different people – be they medical scientists, patients, or healthy volunteers – value the risks and benefits differently. Some may consider certain risks worth taking in relation to potential benefits, while other risks may be viewed as unacceptably high in relation to potential benefits. Assessing risks and benefits has both a scientific component and a personal element. The scientific component is more objective: based on observations, previous studies, and clinical experience, scientists and researchers agree on what risks might be expected, how likely they are to occur, and their impact on morbidity and mortality, and the benefits that are anticipated. At the same time, the risk-benefit assessment has an inherently personal element. Assessing risks and benefits is colored by individual values and the meaning of the risks and benefits in an individual's life or the lives of others. Women's values can differ significantly from those of scientists (whether male or female) in assessing risk-benefit ratios. For example, women's health advocates tend to define the "safety" of contraceptive methods in terms quite different from those typically employed by biomedical scientists.⁹²

Scientists' concern is to establish safety of methods according to specific measurable parameters. They assess toxicity, first in animals and then in carefully controlled studies in human volunteers. Subsequent studies address efficacy and short- to medium-term safety. . . Women's health advocates. . . give more priority to methods that have fewer side effects and that protect against sexually transmitted diseases and their consequences such as infertility. While scientists have tended to give priority to methods which minimize users' control, women's health advocates prefer methods controlled by the users.⁹³

⁹² *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 192.

Thus, including women of childbearing potential in clinical studies evidences a greater acknowledgement of individual values and a respect for personal decision-making.

In addition to the fact that allowing women to participate in clinical trials promotes respect for women’s autonomy and decision-making capacity in reproductive issues, inclusion is arguably constitutionally required. All laws and policies of state and federal government are expected to conform to the U.S. Constitution – the ultimate source of legal authority in this country. The Fourteenth Amendment’s provision that “No state... shall deprive any person of life, liberty, or property” is particularly relevant to questions of participation in clinical research.⁹⁴ The Fourteenth Amendment, and the Bill of Rights in general, have been interpreted by the Supreme Court to require equal access to government health benefits, a high degree of personal liberty in matters affecting health care, and decisional privacy. The Fourteenth Amendment protects the rights to bodily self-determination and personal decision-making about matters closely affecting health. The Supreme Court has upheld the right to decisional privacy with regard to termination of artificial nutrition and hydration⁹⁵ and abortion;⁹⁶ the Court reaffirmed the right to private abortion decision-making in *Planned Parenthood of Southeastern Pennsylvania v. Casey*,⁹⁷ in which it recognized the right of a woman “to choose to have an abortion before viability and to obtain it without undue interference from the State.”⁹⁸ While acknowledging a state interest in the life of at least some fetuses, the Court stressed the importance of reproductive privacy for women’s liberty, linking a woman’s unique reproductive liberty to her ability “to participate equally in the economic and social life of the nation.”⁹⁹ It is difficult to predict what standard of review will apply in future Fourteenth Amendment privacy cases affecting women’s health, including cases involving exclusion from research, because although strict scrutiny was applied in *Roe v. Wade*, rational ba-

⁹⁴U.S. Const. Amend. XIV.

⁹⁵*Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261 (1990).

⁹⁶*Roe v. Wade*, 410 U.S. 113 (1973).

⁹⁷505 U.S. 833 (1992).

⁹⁸*Id.*

⁹⁹*Id.*

sis was applied in *Cruzan*, and an intermediate standard of review was applied in *Casey*. Nonetheless, there is an argument that *Cruzan's* recognition of a right to refuse artificial nutrition and hydration, premised on freedom from intervention in private decision-making related to health care, also implies a right to take part in risky clinical studies; that is, if one can terminate one's own life, one should be able to assume the risk of taking an untested drug.¹⁰⁰

5. Liability for Exclusion of Women

Excluding women from clinical trials has long been viewed as a means of avoiding claims for injuries incurred during the studies, especially injuries to offspring and potential offspring. However, excluding women from clinical trials also bears the risk of liability for pharmaceutical manufacturers and, indirectly, for physicians.¹⁰¹ Manufacturers' liability results when, after a drug is on the market, evidence emerges that the drug is more dangerous or less effective in women. For example, a woman may have an adverse reaction to one of her prescriptions and discover that the drug was never tested in women; the woman's exclusion from clinical research caused the injury. Under strict liability principles, manufacturers may be held liable for the defective design of a product, and a drug that has not been adequately tested may be found to be defectively designed. In addition, manufacturers must warn about not only the known risks of a treatment but also foreseeable risks that should have been known. The duty to warn about foreseeable risks requires

¹⁰⁰R.A. Charo. 1994. "Brief Overview of Constitutional Issues Raised by the Exclusion of Women from Research Trials." In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

¹⁰¹E. Flannery and S.N. Greenberg. 1994. "Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies." In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

that pharmaceutical manufacturers apply state-of-the-art testing methods to their products. With the recent discovery and understanding of physiological differences between men and women with regard to drug efficacy, dosing, and adverse reactions, it would be difficult to argue that all-male studies of drugs that may be used by women represent state-of-the-art testing methods. Also, if the court finds that the manufacturer deliberately avoided learning about whether a risk was associated with its drug, the manufacturer could be liable for punitive damages. Case law suggests that if a drug was found to cause injuries to women but women were excluded from clinical trials of the drug, the pharmaceutical manufacturer might be held liable for failing to test the drug in women.¹⁰²

For physicians, liability resulting from exclusion of women from drug trials arises in the form of negligent drug prescription. For example, the physician could be liable for either prescribing a drug to a woman for a different purpose than that for which it was initially designed and tested or for prescribing a drug in disregard of the drug's label that it has not been tested in women.¹⁰³ Thus, while it may seem less time-consuming and less expensive to investigators to exclude women from clinical studies, in the long run it may be much more expensive to pay for the clinical consequences of not knowing about gender-related differences in drug effects.

B. Rationales for Excluding Women of Childbearing Potential

Despite the fact that the FDA has lifted its 1977 guideline on the exclusion of women of childbearing potential from clinical trials, there remain valid concerns about including this subgroup in human subject research, concerns that go beyond the protectionist policy previously rejected as overly paternalistic. Arguments in

¹⁰²*Id.* at 95.

¹⁰³*Id.*

favor of excluding women from clinical trials include the risk to potential children and the potential for legal liability, problems with recruitment and retention of participants and the increased cost of including women, the negative effect that including women may have on women's health care, and the fact that differences in drug response or drug disposition due to gender are not clinically significant.

1. Risk to Potential Children and Legal Liability

Protecting fetuses and the future reproductive capacity of women with childbearing potential remains a concern for those involved in clinical research and trials. This concern is reflected in the FDA's 1993 guideline by the FDA itself when it stresses the need, where appropriate, for women of childbearing potential to use contraception or abstinence while participating in early trials and sometimes beyond the completion of the study, and the use of pregnancy tests before exposure to the drug. The inclusion of these directives in the guideline indicates lingering concern about the safety of including women of childbearing potential in clinical drug trials. Those in favor of excluding women of childbearing potential from clinical trials argue that potential fetuses and the reproductive capacity of women must be protected by excluding women because possible children cannot consent to their inclusion in clinical studies; consent policies created to protect research subjects do not adequately protect potential fetuses since it is the mother, rather than the child, that consents.¹⁰⁴ In addition, the interests of later generations should be protected by earlier ones. Finally, biologically mediated risks to future human beings are uniquely unacceptable. There is something inherently worse about biologically mediated risks as compared to other risks that social action creates for future human

¹⁰⁴J.D. Moreno. 1994. "Ethical Issues Related to the Inclusion of Women of Childbearing Age in Clinical Trials." In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

generations.¹⁰⁵

Concerns about potential fetuses and the reproductive capacity of women of childbearing potential are compounded by the fear of legal liability if a women suspects that damage to a fetus or gamete was due to participation in a study.¹⁰⁶ The threat of liability exists for injury to any subject of clinical research, but the greatest concern about liability is the possibility of injury to offspring resulting from the mother's exposure either before or after conception due to several factors. First, fear of liability continues to be inspired by the experiences of thalidomide and DES making researchers particularly wary of including women of childbearing potential in early phase drug studies when the effects on both adult and offspring are largely unknown. Second, although it may be difficult for a plaintiff to prove causation, the magnitude of harm that could be alleged to result from in utero exposure to a drug is great. Third, the statute of limitations is usually longer for cases of injury to children, and damage that occurs in utero may not show up until years later, leaving potential defendants liable for an indeterminate amount of time. Finally, legal actions can be extremely costly to defend, even if the plaintiff's case is weak and the question of liability is uncertain, and researchers and drug companies prefer to take action that appears likely to eliminate or reduce the risk of becoming involved in litigation.¹⁰⁷ Although the reported incidences of research-related injuries generally appears to be quite low, fear of liability continues to make researchers apprehensive about including women of childbearing potential in clinical studies.

2. Recruitment and Retention Issues and Increased Cost

¹⁰⁵*Id.* at 30.

¹⁰⁶E.W. Clayton. 1994. "Liability Exposure When Offspring are Injured Because of their Parents Participation in Clinical Trials." *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

¹⁰⁷*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 166.

In addition, including women in clinical trials involves several issues relating to recruitment and retention of study participants.¹⁰⁸ Investigators who wish to recruit and retain women in their studies may encounter problems related to feasibility, logistics, and cost. The NIH Revitalization Act specifically discounts the issue of cost in its requirement that investigators increase the representation of women in their studies, but as a practical issue, the expense of including women in research may limit the extent to which equity in research can be achieved and may prompt more investigators to seek exemptions from requirements of inclusion. The feasibility of recruiting and retaining participants for clinical studies depends on the number of women in the reference population and their characteristics in relation to the study. If eligible women are rare relative to men, or if eligible women in an ethnic, socioeconomic, or age group of interest are relatively rare in comparison with affluent young white women, special efforts will be needed to identify and attract these subjects. The feasibility of studying women is also affected by social conditions that may limit the personal autonomy of women. Women may have less flexibility than men in terms of lifestyle or keeping appointments during work hours. Personal safety may also be a greater concern with respect to evening appointments, which would require the provision of transportation, security guards, and the like. Arranging child care during clinic appointments may be more of a problem when studying women than when dealing with men.¹⁰⁹

Known variations in hormonal status that affect the results of laboratory tests and inference about treatments makes conducting studies that include women more time-consuming and labor-intensive.¹¹⁰ For situations in which menstrual cycle variation or other reproductive variables are related to the issues under study, the feasibility of the study will depend on the ability to schedule or plan around this variability. Finding enough

¹⁰⁸R.J. Levine. 1994. "Recruitment and Retention of Women in Clinical Studies: Ethical Considerations." In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

¹⁰⁹*Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 119.

¹¹⁰*Id.* at 120.

women with the right reproductive or hormonal status and then scheduling around this variability takes time and effort and thus may also increase recruitment costs. Recruiting these women and scheduling around their hormonal variations may also increase sample sizes in order to balance reproductive or hormonal status within the study population. Further, the factors that motivate women to participate in clinical studies, particularly women from different racial and ethnic groups, the elderly, and the poor, may be different from those that apply to men. Similarly, the modes of influence through which women are persuaded to enter and remain in clinical studies may also be culture- or gender-specific.¹¹¹ Including women in clinical trials may therefore require investigators to develop and implement gender-specific recruitment programs, which may in turn require special staffing (for example, elderly women to recruit elderly women into studies) and the costly creation of both new recruitment strategies and the duplication of certain aspects of existing recruitment practices for women as a separate subgroup, and for different racial and ethnic groups within this subgroup. Finally, decisions regarding the appropriateness of individual participation in clinical studies can be influenced by a communal perception of risk and benefit, leading to motivation or resistance to participate based in part on group or community membership.¹¹² For example, African American women may resist participating in research based on stories of covert sterilizations in the past or the exploitation of African American men in the Tuskegee study. Surmounting these community perceptions in order to recruit and retain women may be extremely difficult.

3. Negative Impact on Women's Health

¹¹¹ *Id.*

¹¹² *Id.* at 121.

Policies designed to ensure the inclusion of women in clinical trials of treatment efficacy may be applied so uncritically as to hamper rather than enhance the advancement of scientific information about these groups.¹¹³ The detection of significant differences among relevant subgroups generally requires clinical trials that are prohibitively large, time consuming, and expensive. It has been suggested, for example, that the cost of clinical drug development could double if parallel trials are conducted among men and women.¹¹⁴ Medical researchers may be caught between limited resources and their goal of answering many pressing medical questions. As a result, they may have to sacrifice statistical power in order to allow for complete representation of the subgroups of interest.

4. Gender Differences in Drug Response Are Not Significant

Finally, those in favor of excluding women from clinical trials posit two somewhat conflicting and paradoxical arguments. First, they argue that biologic differences between men and women may reflect genetic, physiologic, lifestyle, cultural and social differences, yet the mechanisms that explain these differences are unknown.¹¹⁵ Without first understanding how these differences are created, it is difficult for investigators to isolate the effects of drugs on subjects when they include both men and women in their research. At the same time, it is argued that differences in drug disposition or drug response due to gender are actually not clinically significant and thus women need not be studied as a special subgroup.¹¹⁶ This argument is based on intersubject and intrasubject variability which patients exhibit in both the pharmacokinetics and

¹¹³R.B. Merkatz, et al., 1993, *supra* note 82.

¹¹⁴*Id.*

¹¹⁵*Id.*

¹¹⁶L.Z. Benet. 1994. "Health Consequences of Exclusion or Underrepresentation of Women in Clinical Studies (II)." In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. Anna C. Mastroianni, Ruth Faden, and Daniel Federman, eds. (Washington, D.C.: National Academy Press, 1994).

pharmacodynamics of drugs. Most drugs on the market today exhibit a wide therapeutic index; major differences exist between the doses, blood concentration, or receptor concentration necessary to achieve a positive therapeutic response versus those amounts that elicit a toxic response. Even if these drugs are only tested in men, there is enough intersubject variability inherent in the male population that the differences between the male and female patient populations are already encompassed by the variability within the male population. Thus, excluding women from clinical trials of drugs with wide therapeutic indexes will not have negative health consequences for women.

Other drugs critical to health care exhibit a narrow therapeutic index; small changes in dose or concentration can shift a patient from an efficacious state to a toxic condition or a state where no efficacy is exhibited. While many drugs exhibit substantial intrasubject and intersubject variability, all narrow therapeutic index drugs, by definition, must exhibit low intrasubject variability. If this were not so, a patient maintained on a particular dose would experience cycles of efficacy, lack of efficacy, and toxicity during a constant dosage regimen. In fact, if a narrow therapeutic index drug does exhibit high intrasubject variability, it will not pass Phase II testing during the drug development process, since it would be impossible to show efficacy for a particular dose. However, narrow therapeutic index drugs may, and often do, exhibit marked interpatient variability. As a result, these drugs are titrated in the patient by the clinician to the appropriate dose or concentration. Thus, it is immaterial whether women differ significantly from men in their pharmacokinetics and/or pharmacodynamics since in every case the drug must be individually titrated; excluding women from clinical studies for narrow therapeutic index drugs will not have negative health consequences for women because of this individualized process.¹¹⁷

PART III: Empirical Evidence of Exclusion and Inclusion

¹¹⁷*Id.* at 42.

The historical evolution of policies and regulations concerning the participation of women in clinical trials and the arguments and rationales for and against including women of childbearing potential in clinical trials must be considered alongside the available evidence concerning whether women have participated in the whole of clinical studies to the same extent as men, and whether women have been disadvantaged by policies and practices regarding their participation or by a failure to focus on their health interests in the conduct of research. Unfortunately, despite the growing literature on women and biomedical research, attempts to determine women's participation in trials and the consequences of previous and currently existing policies and regulations have been hindered by a scarcity of reported data.¹¹⁸ The sources of information available vary widely in scope and method, and while all provide some kind of data on women's participation in clinical studies, many do not provide the kinds of information necessary to make a judgment about the appropriateness of the reported study composition (for example, condition under study, percentages of male and female subjects included in studies of conditions affecting both males and females, adequacy of sample size to analyze gender differences). In addition, much of the available evidence may be colored by the publishing preferences of both authors and editors.

The findings and conclusions of research on women's participation in clinical studies conducted between 1977 and 1993 are insufficient to allow for any definitive conclusion as to whether women in the past have been systematically excluded from or underrepresented in clinical trials to their detriment. Some studies found that an appropriate number of women were included in specific study populations and that more female-only than male-only studies were being conducted. Others found that women were over- or underrepresented in certain types of studies. Still others found that women – especially the elderly and poor women – were less likely to be included in studies than men.¹¹⁹ Based on these studies it is impossible to conclude that women

¹¹⁸ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 47.

¹¹⁹ *Id.* See Appendix.

have or have not actually participated in clinical research. The Appendix summarizes the findings of the studies conducted between 1977 and 1993 on women's participation in clinical trials.

Although it cannot be established that gender inequity existed in the whole of past clinical research, there is evidence that women have been excluded or included in numbers too small to yield meaningful information about their treatment in the areas of AIDS and heart disease research. In both of these areas, there is clear evidence that women have either been excluded altogether or included in numbers too small to yield meaningful information about their treatment. Several well-known studies of cardiovascular disease have not included any female participants. These include the MRFIT, the Coronary Drug Project (CDP), Lipid Research Clinic, and the Physicians' Health Study, all of which have had widespread influence on the treatment and prevention of heart disease. MRFIT (1977) was a study of 12,866 men between the ages of 35 and 57, designed to assess the efficacy of intervention for individuals at high risk for coronary heart disease because of elevated serum lipids, hypertension, and cigarette smoking. CDP (1986) was a randomized, controlled clinical trial designed to evaluate the efficacy of several different lipid-influencing drugs in prolonging the lives of men with a prior history of myocardial infarction. The Physicians' Health Study (1989) was a randomized controlled trial of 22,071 male physicians designed to determine whether low-dose aspirin therapy decreases the risk of myocardial infarction and whether beta-carotene reduces the risk of cancer. Because these studies did not include women, they could not produce definitive information about prevention and treatment of heart disease in women. The extrapolation to women of the male-generated findings of MRFIT, CDP, and PHS is faulty because it ignores the importance of estrogen in women as an antiatherogenic agent and because the natural history of coronary heart disease is different in men and women.¹²⁰ Further, such gender-exclusive research reinforces the myth that cardiovascular disease is a uniquely male disease when in fact cardiovascular disease is the leading cause of death for both men and

¹²⁰*Id.* at 64.

women.¹²¹

Studies show that women have also been underrepresented in AIDS research.¹²² Despite the fact that the first cases of AIDS in women were reported in 1981 and the number of these cases has been increasing rapidly since 1986, it was only in 1994 that comprehensive studies looking at the epidemiology of the disease in women began to be conducted. In clinical trials of AIDS drugs, which often provide significant sources of first-rate medical care and access to experimental treatments for persons with AIDS, the number of women participating has lagged behind expectations for a disease that is increasing rapidly among women. More importantly, where women have been the focus of clinical research, the primary research question has been how to reduce or prevent a vertical transmission of human immunodeficiency virus (HIV) from a pregnant woman to a fetus or newborn, not how to treat the female-specific manifestations of HIV diseases. Further, until recently, there has been almost no research explaining the mechanisms of male-to-female transmission of HIV and little research directed at the development of antiviral preparations that could be used by women to reduce their chances of contracting the infection through sexual activity.

Conversely, the most recent studies I was able to locate on women's participation in clinical research indicate that women are participating in clinical trials equally with men. The Center for Drug Evaluation and Research (CDER) conducted a retrospective review of clinical trial protocols and labeling for 185 new molecular entities approved by CDER between January 1, 1995 and December 31, 1999.¹²³ Enrollment data were derived from medical officers' reviews and tabulated according to gender, while approved product labeling was searched for statements related to product use in humans. Specifically, the study found that overall, women appear to participate in clinical trials at nearly the same rate as men even when gender-specific

¹²¹ *Id.*

¹²² *Id.* at 66.

¹²³ B. Evelyn, T. Toigo, D. Banks, D., D. Pohl, K. Gray, B. Robins, and J. Ernat. 2000. "Women's Participation in Clinical Trials and Gender-Related Labeling: A Review of New Molecular Entities Approved 1995-1999," *FDA/Center for Drug Evaluation and Research* (visited February 2002) <<http://www.fda.gov>>.

products are excluded. A total of 493,600 individuals were described in the medical officers' reviews as being enrolled in the 2,581 clinical trials for all products examined in the study. Gender could be determined from the medical officers' reviews for seventy-four percent of the participants; of these, forty-nine percent were female and fifty-one percent were male. When gender-specific products such as those for ovarian or breast cancer were excluded from analysis, forty-eight percent of participants in clinical trials were female and 52 percent were male. Some differences in participation were found from year-to-year; women appeared to be represented least in 1995 and most in 1996. However, when they evaluated only those participants for whom gender could be determined and eliminated those enrolled in gender-specific products, the authors found women comprised forty-two percent of participants in 1995, fifty-one percent in 1996, forty-four percent in 1997, fifty-five percent in 1998 and forty-four percent in 1999. The study also found that of the 185 product labels reviewed, sixty-eight percent contained some statement related to gender, twenty-seven percent of which indicated that there was no difference between the genders, and twenty-two percent of which described actual gender differences. Of the products for which labeling described gender effects, none required a change in the dosage based on gender differences. The authors of the study concluded that women are participating in clinical trials of new drugs in approximate proportion to their representation in the population and that the majority of product labeling contains references to gender evaluation.

A study by Meinert, Gilpin, Unlap, and Dawson looked at clinical trials published between 1966 and 1998 in U.S. journals and indexed in MEDLINE.¹²⁴ In 1998, sixty-five percent of the 8,903 trials identified involved males and females, ten percent involved males only, 11 percent involved females only, and the remaining fourteen percent could not be classified as to gender mix. The study found that the majority (sixty-four percent) of heart trials involved both men and women and that differences seen for heart disease and HIV trials are in directions consistent with male-female disease burden. In the case of neoplasms, female-only

¹²⁴C.L. Meinert, A.K. Gilpin, A. Unlap, and C. Dawson, C. 2000. "Gender Representation in Trials," *Controlled Clinical Trials* 21: 462-475.

trials outnumbered male-only trials 2.56 to 1, increasing to 3.16 to 1 when breast and prostate trials were removed. The authors concluded that, overall, there was little support for the perception that women have been underrepresented or understudied in trials or that there is an effort bias in favor of men. The authors also argue that as far back as 1979, evidence was against the perception that women were being underrepresented and understudied. They note that of the 986 trials listed as ongoing in NIH's 1979 inventory of clinical trials, eighty-one percent involved both males and females, and that among the remaining trials, there were more female-only than male-only trials. Finally, the authors believe that changes in the gender mix of trials cannot be attributed to the policy and regulatory changes of the 1980s and 1990s because the biggest change in the mix of published reports occurred prior to those events; the ratio of female-only to male only trials jumped from 0.53 for the decade 1966-1975 to 0.89 for the following decade. Thus, not only is the evidence regarding the actual participation of women of childbearing potential in clinical trials inconclusive, but the reasons for changes in women's participation, according to these authors, is also not clearly understood or fully explained by policy changes over time.

PART IV: Analysis of Regulations, Policy, and Rationales

The arguments and rationales for and against including women of childbearing potential in clinical trials indicate that there is no simple answer to the question, "Should women participate?" Rather, the previous discussion indicates that the answer to this question involves considering a multitude of legal, ethical, and physiological issues against a backdrop of policies and regulations. The answer to this question is made more complex when the cost of subgroup analysis is taken into consideration. The issue of participation is muddled further due to popular opinion which influences policy and regulation, opinion which may exist independently of any actual facts about women's participation in research and women's health in general. The current regulatory system does not require the FDA to include women in clinical drug trials. Despite

the fact that the NIH Revitalization Act and the FDA's 1993 guideline require and encourage respectively the inclusion of women in clinical drug trials, neither of these provisions carries the force of law for the FDA. However, a regulation legally requiring the FDA to include women in clinical research does not seem to be necessary at this time. As noted by the FDAMA Women and Minorities Working Group, current regulations and policies seem to ensure that women are sufficiently included in clinical trials. Federal law requires the analysis of effectiveness and safety data for women in NDA applications, and this law is supported by an FDA guideline; the clinical hold rule allows the FDA to place a clinical hold on studies that exclude women; and an FDA guideline emphasizes the importance of including women and evaluating drug effectiveness in this subgroup. These regulations and policies are strengthened by the NIH Revitalization Act which allows NIH to deny funding to studies that exclude women.

Taken together, these regulations and policies appear to ensure that women are included in clinical trials. In addition, although the NIH Revitalization Act requires the inclusion of women while the FDAMA does not, these two regulations are not contradictory. Rather, these regulations are harmonized by the fact that the FDAMA requires the participation of women to be studied in effect to determine whether the FDA itself needs a rule analogous to the NIH Revitalization Act and applying directly to FDA trials. If it is determined under the FDAMA that no further guidance is needed, as it was in 1998, the NIH Revitalization Act serves as a check against this finding, ensuring that women are in fact being included, at least in the trials NIH funds or sponsors. The NIH Revitalization Act does provide wide latitude for exemption from the requirement that women must be included in NIH-funded trials. Nonetheless, according to empirical evidence, it does not appear that women are in fact being widely excluded or understudied in clinical drug trials, indicating that exemptions are not being widely sought by investigators or widely granted by NIH. If women are in reality sufficiently participating in clinical trials, then the FDAMA seems like an effective reg-

ulation. Though it requires neither inclusion nor exclusion, it ensures that the issue of women's participation in clinical trials will be periodically considered and that guidance will be issued as needed. This means that if studies conclusively reveal that women, in the future, are being excluded from trials, steps may be taken to remedy the situation.

Thus, the current regulatory system, supported by federal policy, seems to support and promote the inclusion of women in clinical trials and the results of studies indicate that women are in fact being included. The weight of scientific evidence supports the inclusion of both genders; the differences in drug effects and responses due to gender differences is persuasive evidence that for their results to be generalizable to women, drug trials must include women. The fact that most treatments do not differ significantly in their effect by gender reinforces the justifications for a principle of inclusion: if most treatment effects in clinical trials do not differ by gender, it is reasonable to include both genders.

At the same time, while current policy supports the inclusion of women and including women in clinical trials seems both beneficial and necessary due to the differences between men and women, the question remains – “At what cost?” Where there are no anticipated effects by gender, a policy that requires investigators to include sufficient representation of both genders to permit subgroup analyses would require that clinical trials significantly increase their size and proportionately increase their expenses. Regardless of the fact that the FDAMA does not require inclusion, the NIH Revitalization Act requires investigators to both justify any gender or racial exclusions and identify and analyze any gender differences. Even when there are no anticipated effects by gender, women currently must be included unless there is substantial scientific data demonstrating that there are no significant differences between the effects of the intervention or variable under study on this group and the effects on the subjects included in the trial. The Act also specifies that cost is not a valid reason to exclude a subgroup or fail to analyze gender differences. The analysis of gender differences is also supported by the FDA's 1993 guideline; women must not only be included, but subgroup

differences must also be studied. The goals of this Act and the guideline are laudable; investigators should be obligated to be inclusive in their recruitment practices and to justify any departures in the composition of the study population from what might be expected given the characteristics of the problem under investigation. However, there remains a concern that if the Act is interpreted too rigidly, it will make costly and undue demands on the scientific research process and impede the implementation of its noble goal. Clinical trials should include both genders but requiring investigators to enroll sufficient numbers to ensure the statistical power needed to detect unsuspected and implausible gender differences produces little additional information at greatly increased cost. It does not seem that the interests of equity in health research are best served by requiring that every clinical trial be large enough to conduct valid analyses of every relevant subgroup difference, as current policy appears to dictate. The added cost of such analyses may jeopardize the long-term goals of improving scientific knowledge and understanding the health problems of all peoples. Strategies other than clinical trials exist to help devise hypotheses about the differential response of men and women to medical intervention. These strategies may be significantly less costly than large-scale clinical trials that include significant numbers of men and women to detect gender differences in response. Meta-analysis, a set of quantitative techniques for combining data from different studies of the same or similar phenomena, is one such strategy that is inherently inexpensive and particularly useful for detecting subtle associations between interventions and outcomes and between demographic characteristics and drug effects.¹²⁵ Meta-analysis can be used by clinical investigators to detect significant differences between treatment and control groups where sample sizes in individual studies were too small to allow the detection of statistically significant effects. At the same time, meta-analysis may indicate through averaging that an effect that appeared to be significant in one study is actually less significant. Meta-analysis also allows investigators to detect contradictions or discrepancies among groups of studies. With a collection of studies in a particular area of

¹²⁵ *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 1, *supra* note 1 at 101

research, investigators can compare subgroups of studies with divergent findings to detect mediating factors of study design, treatment, context, measurement, or analysis that otherwise might not have appeared noteworthy.

Outcomes research, which involves the systematic study of health impact of an intervention, and specifically pharmacoepidemiologic research, a type of outcomes research designed specifically for the study of drug effects in user populations, is another inexpensive and useful alternative to clinical trials.¹²⁶ The pharmaceutical industry has recently placed renewed emphasis on the use of these nonexperimental, observational, epidemiologic techniques. Postmarketing surveillance is one of several pharmacoepidemiologic techniques used to study the effects of drugs in uncontrolled settings and in larger numbers of people than can be included in the drug development process. Pharmacoepidemiologic studies avoid some of the important shortcomings of clinical trials, specifically the introduction of intervention and observation effects, and the exclusion of effects resulting from the usage of concomitant medications, presence of other illnesses, and lack of patient compliance. Developments in computer technology and health care management have yielded large, automated, multipurpose databases of patient information collected by health maintenance organizations, an important resource for pharmacoepidemiology. Such large databases permit the epidemiologist to collect information on all drug exposures and all major medical outcomes and to take into account major stratifying variables. Where calculated rates of adverse effects among users tend to be unreliable, a structured epidemiologic study can be a powerful tool for qualitatively assessing unexpected adverse events.

Finally, the pharmaceutical industry has also begun using new techniques designed to expedite and enhance the results of drug development. Pharmacokinetic screens, one of these techniques which may be useful in detecting differential responses to drugs between men and women as well as other subgroup differences, can be used during drug development to infer the influence of demographic factors such as age and gender on

¹²⁶*Id.* at 102.

the pharmacokinetics of a drug (the drug's absorption, distribution, and metabolism in the body, and the drug's excretion from the body) and to suggest the likelihood that a drug-drug or drug-disease interaction will occur.¹²⁷ The screening process involves the analysis of drug levels in members of specific subgroups at designated points throughout a Phase III trial. Conducting a pharmacokinetic screen during drug development adds little extra cost to the development process because the necessary data is collected from patients already participating in clinical trials.

These promising strategies may help to dissipate some of the controversy inspired by including women in clinical drug trials and requiring subgroup analysis of gender differences by better balancing the need to study women's health against the cost of such research. More importantly, these strategies can identify gender differences in drug effects and response without requiring that every clinical trial include women and analyze subgroup differences. Because it appears that women *are* in fact participating in clinical trials, requiring their inclusion seems to be an unnecessary and harmful move particularly in light of the fact that alternative methods for understanding gender differences exist.

¹²⁷ *Id.* at 103.

CONCLUSION

Historically women of childbearing potential have been considered a vulnerable population and therefore systematically excluded from clinical trials. As a result, there is a general perception that biomedical research has not given the same attention to the health problems of women that it has given to those of men, and that women may not have benefited from advances in medical diagnosis and therapy because of their lower rates of participation in clinical studies. These perceived inequities have been the focus of public attention and legislative action over the last two decades as women's health advocates and others have challenged the content of the national research agenda.

The historical exclusion of women from clinical drug trials resulted in a scientific paradigm premised on a male norm – the tendency to conceive of men gender neutrally and to perceive their identity and experience as the characterization or standard of what it is to be a person and to portray female differences, where they occur, as deviant.¹²⁸ According to this norm, basic biological differences between the sexes are irrelevant for most scientific research; male-only studies are regarded as the scientific ideal for conducting research in order to ensure homogeneity across the groups being compared; and male physiology becomes the implicit normal standard for judging etiology, physiology, and response to intervention. Female physiology is examined only to the extent that it is supposed to deviate from the male norm. Until the end of the 1980s, little attention was given to sex and gender as valuable and significant variables to be studied in biomedical research, indicating the continued presence of the male norm. In the past decade however, the issue has

¹²⁸J.A. Sechzer, A. Griffin, S.M. Pfafflin. 1994. "Women's Health and Paradigm Change." In: *Forging a Women's Health Research Agenda: Policy Issues for the 1990s* (Jeri A. Sechzer, Anne Griffin, and Sheila M. Pfafflin, eds., 1994).

clearly attracted the attention of the public, government agencies, and the scientific community, and has resulted in new policies and regulations focused on including women in clinical research. Nonetheless, the perception that scientific research is still based on a male norm prevails.¹²⁹

Perception is often times more important than fact, regardless of whether it is right or wrong. The chasm between perception and truth would not be important if not for the fact that perception frequently drives the actions we take and may have serious consequences. In the case of clinical research, and clinical trials in particular, the perception that publicly funded research favors one gender over the other has driven policy and regulations for the past several decades. These policies and regulations currently reflect a shift away from the male norm paradigm and toward a paradigm that conceives of men and women as different yet equally important participants in clinical research. Aligning popular perception with this new paradigm is extremely difficult, yet at the same time crucial to ensuring that clinical research continues to progress efficiently and effectively. In cases of major policy change, the impetus for such change usually comes from organizations outside the government. Nongovernmental actors thus play a primary role in the creation of public policy. If these actors influence policy and regulatory change and these actors continue to perceive that clinical research favors men, they will support and potentially achieve rigid interpretation of current inclusion and subgroup analysis requirements and may even succeed in establishing more stringent requirements, with the ultimate effect of making this type of research prohibitively expensive and time-consuming.

The studies discussed in Part III in general and the conclusions of the 1998 Meinert et al. study, in particular, may indicate that while public perception drives policy and regulatory change, there may be no real correlation between regulations and policies and women's participation in clinical trials. Although it is unclear how reliable these studies actually are, as bias may be prevalent, the studies do not offer results that would seem to reflect the regulatory system at the time the studies were conducted. For example, Meinert's

¹²⁹J.W. Scott. 1993. "How Did the Male Become the Normative Standard for Clinical Drug Trials?," *Food and Drug Law Journal* 48(2): 187-93.

study found that in 1979, when the FDA's guideline encouraged the exclusion of women of childbearing potential from clinical trials, nearly 81 percent of NIH trials included women; Kinney's 1981 study of 50 clinical trials reported in 1979 revealed that young women served less frequently than young men as subjects in premarketing clinical drug trials, but women were not in fact completely excluded.¹³⁰ The participation of women in trials does not necessarily mirror the regulatory system.

It seems possible that the popular perception that women have been excluded from clinical trials in the past and continue to be excluded currently, compounded by the historic use of the male norm in clinical research, prompted the emergence of policy and regulations preferring inclusion, despite the fact that the empirical evidence may not indicate that women have been excluded from health research to their detriment. If women are in fact being included in research, this must be publicized in order to prevent nongovernmental actors from advocating and possibly achieving more stringent inclusion requirements and potentially jeopardizing important scientific research. Thus, it seems that changing the perception that women are being neglected by clinical research to their detriment, rather than changing the existing policy and regulatory system regarding their inclusion in clinical trials, is the area currently most in need of reform. This type of change would ensure that women participate in clinical trials but that such participation would not be so rigidly enforced as to make clinical research prohibitively expensive.

How this perception can be changed is more difficult to formulate. The NIH Revitalization Act of 1993 is one step in this direction. The Act enhances the availability of information about women's participation in clinical studies by requiring the directors of NIH, the Office of Research on Women's Health, and the National Library of Medicine to collaborate in establishing a "data system for the collection, storage, analysis, retrieval and dissemination of information regarding research on women's health that is conducted or supported by the national research institutes."¹³¹ The Act also requires that the data system include

¹³⁰E.L. Kinney, J. Trautman, J.A. Gold, E.S. Vessel, and R. Zelis. 1981. "Underrepresentation of Women in New Drug Trials," *Annals of Internal Medicine* 95(4): 495-499.

¹³¹NIH Revitalization Act of 1993, *supra* note 48.

a registry of clinical trials of experimental treatments that have been developed for research on women's health, as well as information about subject eligibility criteria, gender, race, ethnicity, age, and the location of the trial. These strategies, however, must be supplemented by better efforts to recruit women into clinical trials. Only by encouraging the subgroup that tends to perpetuate the perception of exclusion to participate in clinical trials will the perception actually change. Women are in fact participating but it seems likely that this is not widely known. Thus, by more actively and publicly recruiting women into clinical trials, the scientific research establishment will convey to women that their participation is essential to clinical research and that women are not in fact being excluded to their detriment.

APPENDIX¹³²

Study Author	Coverage	Findings and Author's Conclusion
Reardon and Prescott, 1977	One 1972 volume and one 1974 volume of the <i>Journal of Personality and Social Psychology</i>	Decrease in the percentage of all-male studies; increase in the percentage of all female studies; increase in gender analysis for both-sex studies.

¹³² *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, volume 1, *supra* note 1 at 50.

Kinney et al., 1981	50 clinical trials reported in 1979	Young women served less frequently than young men as subjects in premarketing clinical drug trials. Women are underrepresented in new drug trials
---------------------	-------------------------------------	---

GAO,
1990

50
cur-
rent
NIH
grant
ap-
pli-
ca-
tions

Twenty
per-
cent
of
pro-
pos-
als
pro-
vided
no
in-
for-
ma-
tion
about
the
gen-
der
of
study
par-
tic-
i-
pants;
over
one-
third
of
pro-
pos-
als
in-
di-
cated
that
both
gen-
ders
would
be
in-
cluded,
but
did
not
spec-
ify
pro-
por-
tions;
sev-
eral
pro-
pos-
als

Hooper, 1990	Women enrolled in 5 categories of randomized-control trial	<p>Women appear to be included in trials of AIDS drugs in a proportion that approximates the proportion of people with AIDS who are women.</p> <p>Women appear to be slightly overrepresented in trials of nicotine gum for smoking cessation.</p> <p>Women appear to be underrepresented in clinical studies of antiplatelet drugs for preventing smoking, antihypertensives, and drugs for myocardial infarction.</p>
--------------	--	---

NIH, Na- tional Heart, Lung, and Blood In- sti- tute (NHLBI), 1990	NHLBI- initiated epi- demi- o- logic and pri- mary pre- ven- tion tri- als ac- tive in 1990	Found 2 tri- als in- cluded ex- clu- sively women, 3 in- cluded be- tween 30 and 45 per- cent women, 10 in- cluded be- tween 50 and 58 per- cent women, and 3 in- cluded ex- clu- sively men.
---	--	--

Cotton, 1990	Multiple Risk Factor Intervention Trials (MRFIT), Physicians Health Study, all large trials of cholesterol-lowering drugs that include men only	There are important gaps in knowledge about the medical treatment of women, the elderly, and nonwhite persons despite mounting documentation of differences in drug responses and risk profiles among these cohorts.
Edwards, 1991	Questionnaire sent to 46 of the largest pharmaceutical companies	All 33 respondents reported that they collect data on gender of trial participants and 25 of the 33 reported that they deliberately recruit representative numbers of women for clinical trials.
Study Author	Coverage	Findings and Author's Conclusion
IOM, 1991	907 grants	Twelve percent of grants represented research including only women, 18 percent included only men, 70 percent included women and men. When all grants were considered together, women comprised 53 percent of the total study population.

PMA, 1991	Medicines in development as of December 1991	Noted 263 drugs were under development for use in women (to treat diseases that affect only women, that disproportionately affect women, or are one of the top 10 causes of death in women). Concluded that America's pharmaceutical research companies recognize the unique medical needs of women and are working hard to resolve the difficulties of developing drugs to meet those needs.
Levey, 1991	Clinical trials reported in all January issues of <i>Clinical Pharmacology & Therapeutics</i> between 1981 and 1991	Comparing trials reported in the 1981 and 1991 issues, found a decline in the number of trials restricted to male subjects and a more than twofold increase in the number of trials that included both men and women, but comparing all issues between 1981 and 1991, found no consistent pattern.
Dresser, 1992	Select large-scale NIH sponsored studies	The failure to include women in clinical research is ubiquitous.
Larson, 1994	Research protocols approved by an IRB at a major tertiary care center during 1989 and 1990	Women were not underrepresented in clinical drug trials or other types of research. Age, race, and SES were more likely than gender to be associated with an unjustified exclusion from research protocols.

Gannon et al., 1992	4,952 articles published in sample years between 1970 and 1990 in the areas of developmental, physiological, and social psychology	Significant increases in the number of female authors and participants, significant decreases in sexist language and inappropriate generalizations from males to females, but continued evidence of discriminatory practices.
Gurwitz et al., 1992	All studies of specific pharmacotherapies employed in the treatment of acute myocardial infarction that appeared in the English-language literature between January 1960 and September 1991	Age-based exclusions are frequently used in clinical trials of these pharmacotherapies. Because women outlive men by an average of 7.5 years, they are disproportionately represented in clinical trials.
PMA, 1992	91 clinical trials active in October 1992 of medicines for AIDS and AIDS-related conditions	Of the 91 medicines, 50 included women in human clinical trials.

Study Author	Coverage	Findings and Author's Conclusion
--------------	----------	----------------------------------

GAO,
1992

All
drug
man-
u-
fac-
tur-
ers
that
ob-
tained
FDA
ap-
proval
be-
tween
Jan-
uary
1988
and
June
1991
for
drugs
com-
bin-
ing
new
chem-
i-
cal
prop-
er-
ties

One-
quarter
of
drug
man-
u-
fac-
tur-
ers
did
not
de-
lib-
er-
ately
re-
cruit
rep-
re-
sen-
ta-
tive
num-
bers
of
women
as
par-
tic-
i-
pants
in
drug
tri-
als;
for
more
than
60
per-
cent
of
the
drugs
in
the
sur-
vey,
the
rep-
re-
sen-
ta-
tion
of

PMA, 1992	Orphan drugs under development in October 1992	26 orphan products were in development for diseases that predominantly or exclusively affect women; for all trials of orphan drugs, enrollment of women approximates the prevalence in women of the disease under study. Women are adequately represented in trials of orphan drugs.
Williams and Manace Borins, 1993	160 randomly selected articles from the 1989 <i>New England Journal of Medicine</i>	Medical research in 1989 was seriously gender-biased, and therefore scientifically flawed.
Pham et al., 1992	AIDS Clinical Trial Group (ACTG) clinical trials	Women, intravenous drug users, people of color, and people of low income have been grossly underrepresented among study subjects in ACTG clinical trials.

<p>Charo, 1992</p>	<p>All drug study protocols submitted for review to the Human Subject Committee of the University of Wisconsin in 1989 and 1990</p>	<p>Of 169 studies, 28 excluded fertile women; 22 of those 28 were sponsored by pharmaceutical companies.</p>
------------------------	---	--

NOW Legal Defense and Education Fund, 1993	ACTG clinical trials, 1990-1992	The percentage of female enrollment in these trials increased from 6.5 percent to 7.8 percent between 1990 and 1992. The numbers of women enrolled in ACTG trials are not enough to provide sound and meaningful data on the effects of a given drug in women.
Cotton et al., 1993	ACTG clinical trials, 1987-1990	Women accounted for 6.7 percent of ACTG clinical trials between 1987 and 1990.
Study Author	Coverage	Findings and Author's Conclusion
Long, 1993	ACTG clinical trials, as of January 1993	The percentage of women accrued as ACTG trial participants is slightly less than women's percentage of CDC-reported AIDS cases. Women seem to be represented in ACTG clinical trials in proportion to the incidence of AIDS among women, but women have been underrepresented in trials of drugs for AIDS-related opportunistic infections.
Eichler et al., 1992	Selected 1988 issues of the <i>New England Journal of Medicine</i> , <i>Canadian Journal of Surgery</i> , <i>American Journal of Trauma</i> , and <i>American Journal of Psychiatry</i>	Gender bias is pervasive in medical research.

Meinert, 1993	All (2,801) active proposals, proposals pending further IRB action, and proposals reviewed and completed or terminated within the last two years at Johns Hopkins University	181 protocols (6.5 percent) included only males, 265 (9.5 percent) include only females, and 2,355 (84 percent) included both males and females.
Meinert, 1993	293 trials listed in the 1979 NIH inventory of clinical trials	All but 25 of the trials included both males and females, of those 25, 13 involved females and 12 involved males; all 12 of the female-only trials involved uniquely or primarily female conditions while only 4 of the male-only trials involved uniquely or primarily male conditions.
Meinert, 1993	All papers (38) published in the journal <i>Controlled Clinical Trials</i> since 1981 that describe an actual clinical trial	Only 28 provided explicit statements regarding gender inclusion criteria, and of these 28, only 21 provided exact counts of males and females. Of the total number of subjects in these 21 trials (78,840), 72,951 were males and 5,890 were females.
NIH, National Eye Institute (NEI), 1993	Active NEI-supported clinical trials	In almost all trials, women comprise at least 40 percent of the participants. Significant numbers of women are included in a variety of NEI-supported trials.

Meinert, 1993	All (2,801) active proposals, proposals pending further IRB action, and proposals reviewed and completed or terminated within the last two years at Johns Hopkins University	A higher percentage of male-only studies were arbitrarily male-only (75.2 percent) as opposed to female-only studies that were arbitrarily female-only (21.2 percent).
NIH, NHLBI, 1993	All trials (49) under way at NHLBI as of May 1993	One trial was male-only, 8 trials were female-only, and women's inclusion in the remaining 40 trials ranged from 10 to 75 percent.
Study Author	Coverage	Findings and Author's Conclusion
Bird, 1994	All original articles reporting results of clinical studies in 1990 and 1992 issues of the <i>Journal of the American Medical Association</i>	Found 207 of the 243 studies were related to gender-neutral diseases, and 49 percent of these 207 included between one- and two-thirds women; of the remaining 51 percent, 17 percent were male-only, 6 percent were female-only, 38 percent had one-third or fewer women and 14 percent had one-third or fewer men. Fifteen percent of single-gender studies had no apparent rationale for their single-gender design. Among those studies examining gender-neutral diseases, women were more likely than men to be underrepresented as research subjects.

NIH, National Cancer Institute (NCI), 1993	NCI-supported clinical trials active in 1992	Of 22,483 participants in treatment trials, 12,490 were female and 9,993 were male; of 9,553 participants in prevention trials, 4,727 were female and 4,826 were male.
Murphy, 1993	ACTG clinical trials, 1992	As of August 1992, females comprised 13.2 percent of the total ACTG trial population. For the 20 most recent ACTG trials with significant enrollment, women comprised 15.7 percent of the trial population.
Korvick and Long, 1993	ACTG clinical trials, 1986, 1992	Representation of females in ACTG clinical trials increased from 2 percent in 1986 to over 18 percent in 1992.

<p>FDA, 1993</p>	<p>Phase I and Phase II trials</p> <p>11 new drug applications pending in 1983</p> <p>All drugs approved in 1988</p>	<p>The effect of the 1977 FDA guideline regarding the participation of women of childbearing potential in clinical studies has been that women have generally not been included in Phase I nontherapeutic studies or in the earliest controlled effectiveness (Phase II) studies.</p> <p>Gender distribution of study populations generally approximated condition incidence by gender; males comprised two-thirds of the study population in studies of cardiovascular drugs.</p> <p>Gender distribution of study populations generally approximated condition incidence by gender; studies of two cardiovascular drugs included slightly more men than women; 2 drugs were studied more in males for unclear reasons.</p>
<p>Study Author</p>	<p>Coverage</p>	<p>Findings and Author's Conclusion</p>

<p>Schmucker and Vesell, 1993</p>	<p>All trials reported in <i>Clinical Pharmacology and Therapeutics (CP&T)</i> during the periods 1969-1971, 1979-1981, and 1989-1991, and in the <i>British Journal of Clinical Pharmacology (BJCP)</i> during the periods 1979-1981 and 1989-1991; all drugs approved by the FDA in 1981 and 1991 that were listed in the <i>1991 Physician's Desk Reference (PDR)</i></p>	<p>The percentage of men-only trials reported in <i>CP&T</i> increased from 27 percent to 38 percent from 1969-1971 to 1989-1991; a similar comparison in <i>BJCP</i> from 1979-1981 to 1989-1991 yielded a 5 percent increase. In both journals during these time periods, the percentage of women-only trials declined. Of 68 clinical trials published in <i>CP&T</i> during 1991 that included both men and women, none claimed differences in drug response that were attributable to gender; the majority of trials failed to mention whether or not the data were analyzed for gender differences. The 1992 <i>PDR</i> revealed reservations concerning use during pregnancy, but not in nonpregnant women, for nearly all drugs approved by FDA in 1981 and 1991. Despite efforts to rectify the underrepresentation of women as participants in clinical trials, this practice has continued during the past decade. The absence in the <i>PDR</i> of any contraindications for use in nonpregnant women are difficult to interpret because they may reflect (1) no evidence of gender differences, (2) exclusion of women from test populations, or (3) failure to analyze clinical trial data for gender differences.</p>
-----------------------------------	--	--

Elks, 1993	Nongonadal clinical studies reported in single volumes of three journals: <i>Clinical Pharmacology & Therapeutics (CP&T)</i> (January through June 1992); <i>American Journal of Physiology: Endocrinology and Metabolism (AJP)</i> (July through November 1992); and <i>Hypertension</i> (January through June 1992)	Of 49 studies reported in <i>CP&T</i> , 14 included no women and 2 included no men. The remaining 26 studies had an average of 59 percent males. Of 32 studies reported in <i>AJP</i> , 10 included only men, 1 included only women, and 4 gave no statement of the gender of participants. The 16 remaining studies had an average of 57 percent males. Of 20 studies reported in <i>Hypertension</i> , 8 included no women and 3 were large epidemiological studies with equal representation. The 9 remaining studies had an average of 64 percent men. Frequent systematic exclusion of females has occurred; even in both-sex studies, more men than women are included than would be likely by chance.
Zahm et al., 1994	Cancer epidemiological studies published between 1971 and 1990 in <i>American Journal of Epidemiology</i> , <i>American Journal of Industrial Medicine</i> , <i>Archives of Environmental Health</i> , <i>British Journal of Industrial Medicine</i> , <i>International Journal of Epidemiology</i> , <i>Journal of the National Cancer Institute</i> , <i>Journal of Occupational Medicine</i> , and <i>Scandinavian Journal of Work, Environment and Health</i>	Of a total of 1,233 studies, 562 (46 percent) include only white men while the remaining 671 studies included subjects from other race-gender groups. Of these, 35 percent included white women, but only 14 percent presented any analyses of the women specifically.

Sources

Angell, M. 1993. Caring For Women's Health – What is the Problem? *New England Journal of Medicine* 329 (4): 271-2.

Battino, D. 2001. Trials in Women. *Epilepsy Research* 45: 141-145.

Benet, L.Z. 1994. Health Consequences of Exclusion or Underrepresentation of Women in Clinical Studies (II). In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Bennett, J. C. 1993. Inclusion of Women in Clinical Trials – Policies for Population Subgroups. *New England Journal of Medicine* 329 (4): 288-91.

Bird, C.E. 1994. Women's Representation as Subjects in Clinical Studies: A Pilot Study of Research Published in *JAMA* in 1990 and 1992. In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Buc, N.L. 1993. Women in Clinical Trials: Concluding Remarks. *Food and Drug Law Journal* 48(2): 223-6.

Charo, R.A.. 1994. Brief Overview of Constitutional Issues Raised by the Exclusion of Women from Research Trials. In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Clayton, E.W. 1994. Liability Exposure When Offspring are Injured Because of their Parents Participation in Clinical Trials. In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Cotton, P. 1993. FDA Lifts Ban on Women in Early Drug Tests, Will Require Companies to Look for Gender Differences. *JAMA* 269(16): 2067.

Eckenwiler, L.A. 1999. Pursuing Reform in Clinical Research: Lessons from Women's Experience. *Journal*

of Law, Medicine, & Ethics 2(27): 1073-1105.

Evelyn, B., Toigo, T., Banks, D., Pohl, D., Gray, K., Robins, B., Ernat, J. 2000. *Women's Participation in Clinical Trials and Gender-Related Labeling: A Review of New Molecular Entities Approved 1995-1999*. FDA/Center for Drug Evaluation and Research (visited February 2002) <<http://www.fda.gov>>.

Flieger, K. FDA Consumer Special Report. Testing Drugs in People. *FDA Consumer Special Report on New Drug Development in the United States (January 1995)* (visited February 2002) <<http://www.fda.gov>>.

Food and Drug Administration. *Food and Drug Administration Modernization Act of 1997*. (FDAMA Sec. 115 Clinical Investigations. (b) Women and Minorities). Rockville, MD: FDA.

Food and Drug Administration. Gender Analysis of Data in Biologic Product Applications (last modified April 3, 2001) (visited February 2002) <<http://www.fda.gov>>.

Food and Drug Administration. *FDAMA Women and Minorities Working Group Report*, July 20, 1998 (visited February 2002) <<http://www.fda.gov>>.

Food and Drug Administration. Executive Summary of the 1995 Gender Workshop, (last modified Jan. 30, 2001) (visited February 2002) <<http://www.fda.gov>>.

Food and Drug Administration. 1993. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. Notice, *Federal Register* 59(139): 39406-39416.

Freedman, L.S., Simon, R., Foulkes, M.A., Friedman, L., Gellar, N.L., Gordon, D.J., Mowry, R. 1995. Inclusion of Women and Minorities in Clinical Trials and the NIH Revitalization Act of 1993 – The Perspective of NIH Clinical Trialists. *Controlled Clinical Trials* 16: 277-285.

Gore, S.M. 1995. Inclusion of Women and Minorities in Clinical Trials. *Controlled Clinical Trials* 16: 290-2.

Keville, T.D. 1994. The Invisible Women: Gender Bias in Medical Research. *Women's Rights Law Reporter*, Volume 15, Numbers 2&3, Winter 1993/Spring 1994.

Levine, R.J. 1994. Recruitment and Retention of Women in Clinical Studies: Ethical Considerations. In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2.

A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Mastroianni, A.C., Faden, R., Federman, D, eds. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*. Volume 1 (Washington: National Academy Press, 1994).

Mastroianni, A.C., Faden, R., Federman, D. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*. Volume 2. Workshop and commissioned papers (Washington: National Academy Press, 1994).

Marvin, D.W. October 5, 1998. Impact of Gender on Drug Responses. *Drug Topics* 19(142): 91-111.

McGowan, J.A., Pottern, L. 2000. Commentary on the Woman's Health Initiative. *Maturitas* 34: 109-12.

Meinert, C.L., Gilpin, A.K., Unalp, A., Dawson, C. 2000. Gender Representation in Trials. *Controlled Clinical Trials* 21: 462-475.

Merkatz, R.B. 1993. Women in Clinical Trials: An Introduction. *Food and Drug Law Journal* 48(2): 161-6.

Merkatz, R.B., Temple, R., Sobel, S., Feiden, K., Kessler, D.A. 1993. Women in Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy. *New England Journal of Medicine* 329 (4): 292-6.

Merton, V. 1993. The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. women) from Biomedical Research. *American Journal of Law and Medicine* 19(4): 369-451.

Minkoff, H., Moreno, J.D., and Powderly, K.R. 1992. Fetal Protection and Women's Access to Clinical Trials. *Journal of Women's Health* 1:137-140.

Moreno, J.D. 1994. Ethical Issues Related to the Inclusion of Women of Childbearing Age in Clinical Trials. In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Scott, J.W. 1993. How Did the Male Become the Normative Standard for Clinical Drug Trials? *Food and Drug Law Journal* 48(2): 187-93.

Sechzer, J.A. , Rabinowitz, V.C., Denmark, F.L., McGinn, M.F., Weeks, B.M., Wilkens, C.L. 1994. Sex and Gender Bias in Animal Research and in Clinical Studies of Cancer, Cardiovascular Disease, and Depression. In: *Forging a Women's Health Research Agenda: Policy Issues for the 1990s*. J.A. Sechzer, A. Griffin, and S.M. Pfafflin, eds., (New York, New York: New York Academy of Sciences, 1994).

Sechzer, J.A., Griffin, A., Pfafflin, S.M., eds. 1994. Women's Health and Paradigm Change. In: *Forging a Women's Health Research Agenda: Policy Issues for the 1990s*. J.A. Sechzer, A. Griffin, and S.M. Pfafflin, eds., (New York, New York: New York Academy of Sciences, 1994).

Sechzer, J.A., Griffin, A., Pfafflin, S.M., eds. *Forging a Women's Health Research Agenda: Policy Issues for the 1990s*. (New York, New York: New York Academy of Sciences, 1994).

Weisman, C.S. and Cassard, S.D. 1994. Health Consequences of Exclusion or Underrepresentation of Women in Clinical Studies (I). In: *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Volume 2. A.C. Mastroianni, R. Faden, and D. Federman, eds. (Washington, D.C.: National Academy Press, 1994).

Willis, J.L. 1997. FDA Consumer Special Report. Equality in Clinical Trials: Drugs and Gender. In: *Your Guide to Women's Health*, Third Edition, Office of Special Health Issues (placed on the web Dec. 24, 1997) (visited February 2002) <<http://www.fda.gov>>.