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Sex & Gender: The Politics, Policy, and Practice of Medical Research

Sarah K. Keitt, M.P.H.*

While women generally live longer than men,¹ they often do not live healthier.² Historically, women have suffered from a lack of medical information specific to their needs and problems.³ This information gap is the result of policies and practices that excluded women from participating as research subjects in most clinical trials until the late 1980s. Women were initially excluded from participating in clinical trials due to neglect and, after the Thalidomide tragedy of the 1960s, misguided efforts at protection. It was not until the mid-1980s that the medical research community began to recognize that the information gap created by these policies had a detrimental effect on women’s health and began to take action to fill this gap.⁴

This Article explores issues surrounding women’s participation in clinical trials. Part I outlines the cultural and regulatory norms that for many years resulted in the exclusion of women from clinical trials. It includes a discussion of protectionist regulations, landmark legislation, and the backlash against the women’s health movement. Part II provides

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recommendations for improving the research process to allow for more equitable and scientifically sound research on the health issues that affect women. These recommendations include closer attention to the needs of female research participants, as well as novel methods of study design and data analysis.

I. THE HISTORY OF THE WOMEN’S HEALTH MOVEMENT

A. The Traditional Paradigm

Anyone who has taken a course in human biology, physiology, or pharmacology is familiar with the “Typical 70 Kilogram Man.” Our knowledge of human biology is based on this archetype as the standard human research subject. For decades, biologists and medical researchers approached the study of human biology from the point of view that whatever happened in the “70 Kilogram Man” was the norm, and that anything that differed from that norm, including female biology, was “atypical,” or even abnormal. A quick Medline search shows that this model is still in use; practice guidelines and research examples are often expressed in terms of the 70 kilogram male.

Until recent years, most researchers belonged to one of two camps (and sometimes both): one group saw females as smaller versions of males and thus viewed the study of women as unnecessary; the other group believed that women were too complicated to study because their hormonal cycles made them difficult subjects and led to complicated data. Research results from men were routinely incorporated into treatment guidelines for women, regardless of acknowledged male/female

5. See, e.g., ROBERT L. VICK, CONTEMPORARY MEDICAL PHYSIOLOGY (1984) (using the “70 Kilogram Man” as the standard throughout).
6. See HEALY, supra note 2, at 8.
differences in body fat, hormones, and other physiological functions.

Policies aimed at protecting the fetus and women’s reproductive potential added to this preference for male subjects. In 1962, the Kefauver-Harris Amendment, perhaps the most important piece of legislation regulating the conduct of clinical trials, was passed with the purpose of protecting children, pregnant women, and fetuses. The Kefauver-Harris amendment required drug manufacturers to demonstrate that new drugs were safe and effective via adequate and well-controlled clinical trials. This legislation was passed in response to the thousands of babies born with severely deformed limbs as a result of in utero exposure to Thalidomide. Later, during the early 1970s, research revealed that the daughters of women who took diethylstilbestrol (DES) during pregnancy had an increased risk of vaginal cancer. In 1977, the United States Food and Drug Administration (FDA) responded to these two events by issuing guidelines that required women of childbearing potential to be excluded from drug trials until teratogenicity data from animal studies of the drug were available. The only exception to these guidelines was for drugs used in the treatment of life-threatening or serious diseases. Because teratogenicity studies were usually performed at the same time as clinical trials in humans, these guidelines had the effect of excluding women from most drug trials. When the general acceptance of the male norm was coupled with images of deformed babies, the medical community did not question the exclusion.

B. The Women’s Health Movement: A Sea Change in Public Policy

Despite their commendable purpose, the 1977 guidelines did more harm than good. In 1983, then-Assistant Secretary for Health Dr. Edward Brandt found that while the United States Public Health Service published a great deal of health information on menstruation, menopause,
pregnancy, and breast diseases, there was a lack of information on other conditions, such as heart disease, that affect women. To address this situation, Dr. Brandt appointed a task force on women’s health issues to develop an analysis of women’s health activities and an agenda for further activities. In 1985, the task force concluded that the lack of a research focus on women’s health issues compromised the quality of health information available to women as well as the health care they received. The report’s findings prompted the National Institutes of Health (NIH) to develop guidelines urging the inclusion of women of child-bearing potential in federally funded clinical research. Researchers and women’s health advocates soon became aware, however, that the inclusion guidelines were not enforced and that women were still routinely excluded from clinical trials.

In 1990, researchers and advocates concerned about the inclusion of women in medical research organized into what later became the Society for Women’s Health Research. At the urging of the Society, Congress ordered the General Accounting Office (GAO) to conduct a study into NIH’s policies and practices regarding the inclusion of women. The resulting GAO report disclosed the lack of improvement in the inclusion of women in NIH-funded research. Specifically, the report found that the NIH policy had not been well communicated or understood within NIH or the research community, was applied inconsistently across institutes, and only applied to extramural research. The GAO also found that despite their own published recommendations, NIH officials had done little to encourage the analysis of study data by sex. Finally, the 1990 GAO report concluded that there was no readily accessible source of data on the demographics of NIH study populations. The 1990 GAO report signaled a

15. 15 NAT’L INST. HEALTH, NIH GUIDE FOR GRANTS AND CONTRACTS (1986) (“[T]he NIH urges applicants for grants and offerors for contracts to consider the inclusion of women in the study populations for all clinical research efforts. . . . If women are not included, a clear rationale should be provided for their exclusion.”).
18. Hearing, supra note 16.
19. Id.
landmark moment for women’s health research. Researchers were put on notice that they would be held accountable for upholding previously enacted policies that encouraged the inclusion of women in clinical trials.

Public outrage over the implications of missing information on women fueled the work of congressional champions of the issue. A month after the release of the GAO report, the Congressional Caucus on Women’s Issues introduced the Women’s Health Equity Act of 1990 (WHEA). This legislative response consisted of twenty separate bills designed to improve research on women’s health issues, women’s access to health care, and disease prevention services for women. WHEA’s chief Senate sponsor, Senator Barbara Mikulski (D-MD), attached three provisions to legislation reauthorizing NIH funding which created an office specifically devoted to women’s health research at NIH, required that women be included in clinical trials, and established five contraceptive and infertility research centers. Of all the provisions included in the bill, only two—the Breast and Cervical Cancer Mortality Prevention Act and Medicare coverage for screening mammography—were passed at that time.

Also as a result of the 1990 GAO report and the outcry it provoked in Congress, NIH instituted guidelines for grant submission that required the inclusion of women as research subjects unless there was a clear justification for their exclusion. These guidelines became law in 1993 with the passage of the 1993 NIH Revitalization Act, which contained language requiring the inclusion of women in medical research and the analysis of resulting data by sex. This language differs from the 1985 guidelines, as the earlier guidelines simply encouraged, but did not require, the inclusion of women in clinical trials. By requiring the inclusion of women, the new

21. Id.
25. The 1994 NIH guidelines state that “it is the policy of NIH that women and members of minority groups and their subpopulations must be included in all . . . projects involving human subjects.” Id. at 14,509.
26. The 1994 guidelines stated that “[f]or Phase III clinical trials, [the NIH must] ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished.” Id. at 14,508.
legislation was a major policy shift in biomedical research. Scientists could no longer categorically deny women access to clinical trials; instead they had to provide a scientific argument to justify women’s exclusion.

The 1990 GAO report on the inclusion of women in NIH-sponsored research was followed by a 1992 report on the practices of the FDA in approving prescription drugs. The 1992 report found that while women were sometimes included in drug trials, they were underrepresented. The study reported that “for more than 60 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.” Even when women were included in large numbers, data were not analyzed to determine if women’s responses differed from those of men. Further, drug manufacturers often failed to study whether their drugs interacted with the different hormonal environment of a woman’s body. The report concluded by recommending that the FDA should ensure that drug companies consistently include “sufficient numbers of women in drug testing to identify gender-related differences in drug response and that such differences are explored and studied.”

As a result of this report, the FDA lifted its restriction regarding the inclusion of women of childbearing potential in clinical trials and formalized guidelines regarding the analysis of data by sex.

C. Clinical Trials and the Pregnant Woman

The regulatory changes of the 1990s resulted in greater access to clinical trials for women. By the year 2000, the number of women in federally funded clinical trials was proportionate to their numbers in the general population. The inclusion of pregnant women, however, remained an especially thorny issue. In 1975, the federal regulations governing the use of human subjects in research were amended to reflect a perceived need to afford special protection to fetuses and potential fetuses, effectively treating the fetus as a vulnerable research subject who could not

28. Id. at 2-3.
29. Id. at 12.
give consent. This change had the result of diminishing women’s autonomy in deciding whether to assume the risk of participation in a clinical trial, regardless of whether or not she was pregnant. In 1991, the emphasis shifted from fetal protection to respect for women’s autonomy when the Supreme Court ruled in UAW v. Johnson Controls, Inc. that a woman has the right to be involved in decisions concerning fetal risk. This ruling supported the Pregnancy Discrimination Act of 1978, which stated that decisions about the welfare of future children should be left to the parents who conceive, bear, support, and raise them. In both instances, the Court and Congress supported a woman’s ultimate right to make the decision about accepting risks that may be potentially harmful to her reproductive status. Assuming that a woman is given appropriate risk information, one would assume that she is as capable of making decisions about participation in clinical trials as she is of making decisions about employment.

In May of 1998, during the Clinton administration, the United States Department of Health and Human Services (HHS) published a proposed change to federal regulations that would have allowed pregnant women to be included in clinical trials. Essential to this rule was the policy of not requiring paternal consent for a pregnant woman to participate in research. In reviewing the Proposed Rule, organizations such as the National Task Force on AIDS Drug Development, the Presidential Advisory Council on HIV/AIDS, and the Institute of Medicine’s Committee on the Ethical and Legal Issues Relating

35. See Merkatz, supra note 33, at 274.
36. 45 C.F.R. pt. 46.
38. The issue of paternal consent will be discussed in more detail below. See infra Section II.D.
to Inclusion of Women in Clinical Studies, agreed unanimously that the participation of pregnant women in research should not be conditioned on paternal consent. The Final Rule, which was published in January 2001, concluded “the decision making authority for research participation of the pregnant woman or fetus prior to delivery should rest with the pregnant woman.” By making the pregnant woman the sole decision-maker, the regulation based the participation of pregnant women in research on a policy of presumed inclusion, rather than presumed exclusion.

Scheduled to take effect in March 2001, this regulation was delayed as the incoming Bush administration considered several modifications, one of which specifically addressed paternal consent. The proposed modification would have required a father’s consent for participation in research that was directed solely at the fetus and that would not affect the mother’s health. The father’s consent, however, would not be needed for a woman to participate in research that would benefit her own health.

This distinction is largely apocryphal as one cannot generally separate the health of the mother from that of the fetus. As one policy expert stated, “Fetuses may be more vulnerable than adults, but no hazards affect exclusively fetuses.”

After reviewing public comment on the modification, HHS adopted the modification into the final replacement rule on November 13, 2001 and retained the language specifying that paternal consent would be required for participation in research directed solely at the fetus. The final rule did add language specifying that paternal consent is not required in the case of rape or incest and that only maternal consent is needed for participation in research that may benefit both the mother and the fetus or only the mother. In cases where research is aimed only at the fetus, paternal consent is required for participation.

41. Id. at 3880.
43. Id.
44. Id. at 56,776.
D. Criticism of the Women's Health Movement and the Response to that Criticism

As a result of legislation and policies to make medical research more widely available to women, the number of women included in clinical trials has increased. As mentioned above, a report issued by the GAO in 2000 found that women are being included in clinical trials at rates proportionate to their numbers in the general population. The report found that "the review process for extramural research now treats the inclusion of women and minorities as a matter of scientific merit ... and it appears that NIH staff and researchers are working to ensure that, when appropriate, study findings will apply to both women and men." With success, however, comes criticism. Critics cite the increasing numbers of female participants in NIH-funded clinical trials as evidence that attention to women's health has come at the expense of attention to men's health. Many of these critics have based their arguments on the findings of a 2000 study by Curtis Meinert, which concluded that prior to 1993, women had not been excluded from clinical trials. However, the findings from this single study are contradicted by those of several other studies that did find a bias against the inclusion of women in clinical trials but did not gain as

47. See U.S. GEN. ACCOUNTING OFFICE, supra note 31.
48. Id. at 2.
51. See EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH, supra note 49; Satel, supra note 49; Young, supra note 49; Bartlett, supra note 49.
52. Kathryn Graff Low et al., Women Participants in Research: Assessing Progress, 22 WOMEN'S HEALTH 79-98 (1994); Mary McGraie McDermott et al., Changes in Study Design, Gender Issues, and Other Characteristics of Clinical Research Published in Three Major Medical journals from 1971 to 1991, 10 J. GEN. INTERNAL MED. 13-18 (1995); Douglas L. Schmucker &
much exposure in the popular press as did Meinert’s.

Meinert also asserts that “within broad limits, treatments shown to work in one gender group also work in the other gender group.” This conclusion was soundly refuted in the Institute of Medicine’s 2001 landmark report, Exploring the Biological Contributions to Human Health: Does Sex Matter? In the mid-1990s, a consortium of public and private sponsors, led by the Society for Women’s Health Research, initiated and sponsored the formation of the Institute of Medicine’s (IOM) Committee on Understanding the Biology of Sex and Gender Differences. The Committee was charged with considering the biology of sex at the cellular, developmental, organ, organismal, and behavioral levels. The IOM report concluded that:

There is now sufficient knowledge of the biological basis of sex differences to validate the scientific study of sex differences and to allow the generation of hypotheses. . . . Naturally occurring variations in sexual differentiation and development can provide unique opportunities to obtain a better understanding of basic differences and similarities between and within the sexes.

Figure 1 provides a list of a few of the sex differences highlighted in the IOM report.

The exploration of sex differences in medical research is not purely an academic concern. Missing information on sex differences has serious health implications for women. A 2001 report by the GAO found that eight of ten prescription drugs that had been withdrawn from the United States market since January 1997 caused serious adverse reactions more often in women than in men. Four of these drugs were prescribed with equal frequency to men and women, suggesting that the greater health risks in women were possibly due to physiological differences between women and men that predispose women to some drug-related health risks, including


54. See EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH, supra note 49.

55. See id. at 3.

Torsades de Pointes (TdP), a potentially fatal cardiac arrhythmia (Table I). 57

Other studies support the GAO findings. For example, one study found that the commonly prescribed antibiotic erythromycin causes TdP more often in women. 58 The investigators concluded that greater serum concentrations of erythromycin in women were not to blame for the increased risk of TdP; rather, the rate of erythromycin metabolism is higher in women, thereby mitigating the differences in body size and blood volume. 59 Some experimental studies have suggested that sex hormones, such as estrogen, can alter myocardial repolarization, potentially prolonging the QT interval, 60 leading to TdP. 61 Other studies, however, suggest that the effects of estrogen are not likely to be responsible for the gender differences seen in myocardial repolarization. 62 Conflicting findings such as these highlight the need for further research in the field of sex-based biology.

Sex differences in drug metabolism have serious implications for the drug development and approval process. For example, in one study of steroid-dependent Crohn’s disease, researchers used separate parameters for drug clearance (the rate at which the body metabolizes a drug)—one for males and one for females. 63 They also used covariants such as lean body weight to take into account the volume of drug distribution. They found that for a given dose of the study drug, males in the study had a

57. Id. at 2-4.
59. Id. at 1776.
60. The QT interval is a measurement made from the electrocardiogram (ECG or EKG). It reflects the duration of the electrical activity that controls contraction of the cells of the heart muscle. For more information, see Ariz. Ctr. for Educ. & Res. on Therapeutics, Commonly Asked Questions, at http://www.qtdrugs.org/consumers/ask-expert.htm (last visited Jan. 21, 2003).
61. Milou-Daniel Drici et al., Sex Hormones Prolong the QT Interval and Downregulate Potassium Channel Expression in the Rabbit Heart, 94 CIRCULATION 1471, 1473-74 (1996); M. Pragnell et al., Estrogen Induction of a Small, Putative K+ Channel mRNA in Rat Uterus, 4 NEURON 807 (1990).
lower maximum concentration of the drug than did females. Further, they concluded that weight normalization for dosing did not provide for equal exposure for this particular drug and that dosing should have been stratified by sex. Despite this important information, the study sponsor did not want separate dosing recommendations for males and females for fear it would be more difficult to market the drug with differential dosing. As this drug failed to show efficacy at a single dose, the study sponsor elected not to market it.

In another study, a lipid protease inhibitor failed to show efficacy in reducing damage from infarcts of the brain. When looking at the pharmacokinetic (PK) and pharmacology data in retrospect, however, there is reason to believe that the women in the study were simply under-dosed. The clearance rate for the drug was 149 percent greater in women than in men, meaning that on average, for a given dose, women achieved only two-fifths the blood, tissue, and brain levels of the drug that men did. In this case, the study sponsor decided not to move forward with developing the drug and a potentially beneficial therapy was lost.

As demonstrated by these examples, the inclusion of more women in clinical trials without appropriate analysis of data by sex serves political purposes but does little to improve our knowledge of women's health. The 2001 reports from the IOM and GAO emphasize that analyzing data by sex is critical for advancing our knowledge of human health.

II. POLICY SUGGESTIONS AND IDEAS FOR THE FUTURE

A. Improving Recruitment and Retention

Women are now increasingly included in clinical trials, but much can still be done to encourage women to volunteer for and remain in trials. Research has found that public misperceptions, mistrust of medical research, and fear of clinical trials are major barriers to participation in trials for both men and women. Potential subjects often believe that participating in a research trial means that they will receive general

64. Id.
65. Id.
67. Id.
medical care. They may be disappointed to learn that they are only receiving medical care related to the study. Additionally, participants may drop out of a study if they believe they are receiving a placebo or less efficacious form of a drug or therapy. The fear of numerous visits, unpleasant side effects, or complicated regimens that can interfere with work or family responsibilities can also prevent women from enrolling in medical studies. Examples of research misconduct, such as the infamous United States Public Health Service Syphilis Study (known as “The Tuskegee Study”) have led to fear and distrust of the medical system, resulting in lower enrollment rates. To address this problem, investigators and recruiters must be frank with participants about the specifics of a study, realistic about the expected costs and benefits from the trial, and focused on conducting a trial safely and ethically.

Researchers often cite the difficulty of recruiting and retaining female subjects in clinical trials as one reason why women are not sufficiently included in studies. Beyond the barriers mentioned above, there are additional barriers that are of special concern for women. These include lifestyle and logistical issues, concerns about participation risks, potentially onerous requirements for fetal protection, and unmanageable time commitments required by the study protocol. Traditionally, women have been the primary caregivers for family members. As such, participation in a clinical trial may significantly impact a woman’s ability to care for her family. Minimizing time and safety barriers for women can have a significant effect on increasing their participation in clinical trials.

Overcoming lifestyle and logistical issues requires that investigators consider critical questions during the study planning and implementation phases such as:

- Has study protocol minimized the number of study visits?
- Is the site open evenings or weekends?
- Can the site provide childcare during study visits?
- Does the site offer convenient parking and access to public

70. Id.
transportation?
- Is the site located in a safe area?
- How can long waiting times during visits be reduced or avoided?

Further, investigators should be cognizant of the potential impact of a study on a woman’s responsibilities in the home.

Study sites that have successfully retained women have done so by paying close attention to women’s needs and concerns. Female participants value the relationships they develop with study staff and appreciate staff attention to events in their lives. Fostering such a relationship can be done with little added expense by simply taking note of events that a study participant mentions during visits. These may be family events such as births, illnesses or deaths, or an upcoming vacation or anniversary. Other strategies may include sending birthday cards or valentines to participants, or creating newsletters and other ways to maintain contact between study visits. Even in populations of hard-to-reach women, attention to their special needs results in exceptional retention rates. In one study of an HIV prevention and vaccine trial, researchers had a retention rate of ninety-two percent after the first year of the study. What makes this retention rate so exceptional is that the study population consisted of poor, disenfranchised women, many of whom had moved repeatedly, or were using illegal drugs. The researchers attributed their success to the support they provided these women in the form of a shoulder to cry on, toiletries for the homeless and incarcerated, and referrals to social services for housing, drug treatment, domestic violence, welfare or other services. In addition, they concluded that study design requires one full-time staff person whose job was to focus solely on retention issues.

To overcome public fears and misperceptions of medical research among both men and women, organizations and agencies have initiated

73. Id.
75. See Richardson, supra note 68.
76. Id.
79. See Brown-Peterside, supra note 77, at 1378.
public education efforts and organized on-line resources for locating studies. NIH maintains a database of all federally-funded research studies. Patients and potential study participants can search this database at www.clinicaltrials.gov. On-line listings of clinical trials and information on participating can also be found at www.womancando.org and www.centerwatch.com. All three websites contain information about what clinical trials are, who can participate, and how to make a decision about participating.

There is early evidence that web-based education may increase enrollment rates. Results from a recent Harris Poll and Boston Consulting Group study show that the more frequently a patient uses the Internet to seek health information, the stronger his/her response to "the call to action issued by health care companies." The researchers found that "those who use the Internet frequently are two to three times more likely than infrequent users to take action that affects their diagnosis and treatment." Logic would dictate that the more often patients use the Internet to research clinical trials, the more likely they are to participate.

It is important to note that strategies for promoting the recruitment and retention of women in clinical trials can be applied to other under-represented populations such as minorities and the elderly. Specifically, effective recruitment and retention strategies will take into account the knowledge, attitudes, and beliefs of potential study volunteers, as well as an assessment of potential barriers to continuing participation once a volunteer is enrolled. For example, extensive outreach by investigators to community leaders can help to overcome mistrust within minority communities. Researchers must be aware that normal effects of aging (for

80. The Society for Women's Health Research's "Some Things Only a Woman Can Do" public education campaign (www.womancando.org) provides tools for physicians and researchers to educate potential study volunteers about research and participation in studies. The campaign distributes printed information (available by calling a toll-free number), maintains an Internet site, and coordinates outreach to the print and broadcast media to reach women throughout the United States.


82. Id.

83. Katherine Pitkin Derose et al., Dealing with Diversity: Recruiting Churches and Women for a Randomized Trial of Mammography Promotion, 27 HEALTH EDUC. BEHAV. 632, 643-44 (2000); Shawkat Dhanani et al., Community-based Strategies for Focus Group Recruitment of Minority Veterans, 167 MIL. MED. 501, 504 (2002); Marion K. Slack et al., Strategies Used by Interdisciplinary Rural Health Training Programs To Assure Community Responsiveness and Recruit
example, vision problems and mobility issues), chronic disease, transportation needs, negotiations with caretakers such as family members, and physician involvement can all impact recruitment and retention of elderly subjects. It has become obvious that a one-size-fits-all approach to recruitment and retention will limit a researcher’s ability to recruit a diverse study population.

B. Informed Consent and the Use of Contraceptives

For any woman, pregnant or not, a thoughtful and honest informed consent process is critical to increasing the participation rate of women in clinical trials. During the informed consent process the research staff is responsible for informing a woman of potential risks to both her and her potential fetus and providing her with information about all available options in the event of pregnancy. A 1999 study found, however, that “investigators often omit fetal risk information from consent documents.” Without full disclosure of fetal risks, a woman of childbearing potential is unable to make a truly informed decision about her enrollment in a clinical study.

Concern about fetal risk may also lead to enrollment requirements that pose an undue burden on female participants, such as the use of contraception methods that the participant may not find acceptable or affordable. Researchers and study sponsors often struggle with how to communicate risk effectively, and one means of reducing risk in cases with clear evidence of fetal risk, or with an unknown potential for risk, is to require women who are heterosexually active and who are not surgically sterile or postmenopausal to use effective contraception. This approach, however, limits access to trials for women who do not use birth control for economic, medical, moral, or religious reasons. Further, there may be limitations to what constitutes “effective” contraception. For example, hormonal contraception may alter the pharmacokinetics and pharmacodynamics of the drug being studied and may make it difficult to

Practitioner, 16 J. INTERPROF. CARE 129 (2002).
84. Elizabeth A. McNeely & Sandra D. Clements, Recruitment and Retention of the Older Adult into Research Studies, 26 J. NEUROSURGERY NURSING 57, 58-59 (1994).
separate the side effects of the study medication from the side effects of hormonal contraception. Certain drugs can also alter the effectiveness of hormonal contraceptives. Unfortunately, non-hormonal contraceptive methods such as condoms, diaphragms, periodic abstinence, and withdrawal have failure rates between thirteen and twenty-eight percent.

An important study found that informed consent documents routinely spelled out the requirement that female participants use contraception, but did not provide adequate justification for such a requirement. When a study does require the use of contraception, the explanations for this requirement should be offered in a manner that is respectful of a woman’s autonomy in deciding which contraception methods to use. Women for whom contraceptives would be an unnecessary burden (for example, religious women who have taken vows of celibacy, women whose partners have been surgically sterilized, and lesbians) should not be required to use them. If the study involves compulsory pregnancy testing, this requirement should be clearly explained to women during the consent process.

C. Pregnancy and the Clinical Trial

Because women of reproductive potential are now included in clinical trials, there is the potential for some of these women to become pregnant while participating in a study. Pregnancy during a clinical trial opens up new concerns and risks—including practical issues such as the unknown effects of pregnancy on the pharmacokinetics and pharmacodynamics of a drug, and the ethics of continuing the administration of a study medication with unknown reproductive risks. However, the 1994 report from the IOM concluded that the lack of information regarding safe treatment options for pregnant women has its own set of concerns and risks. The Committee recommended that “NIH strongly encourage and facilitate clinical research to advance the medical management of pre-existing medical conditions in women who become pregnant (e.g., lupus), medical conditions of pregnancy (e.g., gestational diabetes), and

90. Joanna Cain et al., Contraceptive Requirements for Clinical Research, 95 OBSTETRICS & GYNECOLOGY 861, 861 (2000).
91. See Hammerschmidt, supra note 86, at 12.
conditions that threaten the successful course of pregnancy (e.g., pre-term labor).\textsuperscript{92} As outlined in the Belmont Report, the principal of respect for persons requires that research subjects be given the opportunity to choose what will and will not happen to them.\textsuperscript{95} Therefore, a truly informed participant, aware of the potential risks to her and to her fetus, should be allowed to make her own decisions about continuing in a study. It is more unethical to deny her the autonomy to make her own medical decisions than it is to force her to quit in the name of fetal health.

\subsection*{D. Paternal Consent}

The regulation discussed above requiring paternal consent before a pregnant woman can participate in a trial aimed at the health of the fetus\textsuperscript{94} is based on the assumption that one can separate the mother’s health from that of the fetus. Arguments for requiring paternal consent were summarized in a 1994 IOM report:

The committee recognizes that the husbands of pregnant women, as well as future fathers who are not husbands, have an interest in the health of their children and that these men may have a deep emotional attachment toward their offspring prior to birth. Until a child is born however, the future father can only protect the health of the potential child by controlling the decisions and actions of the woman.\textsuperscript{95}

The IOM concluded that “[t]o give men the authority to veto the decisions of their wives or partners to participate in research grants men unacceptable power over women.”\textsuperscript{96} This position is also supported by the Scientific and Ethical Review Group (SERG) of the World Health Organization, which stated, “A requirement of partner agreement or authorization for an individual to participate in research violates the autonomy of research subjects and their right to confidentiality.”\textsuperscript{97} By

\begin{itemize}
  \item \textsuperscript{92} Women and Health Research, \textit{supra} note 87, at 16.
  \item \textsuperscript{95} Women and Health Research, \textit{supra} note 87, at 197.
  \item \textsuperscript{96} Id.
\end{itemize}
requiring paternal consent for participation in medical research, one is denying a woman the autonomy to make decisions about her health and about what is to be done to her body.

E. Improving Statistical Design in Clinical Trials and the Need for Accurate Drug Labeling

As discussed above, sex differences in drug trials may be missed in early phase clinical trials because women are not included in numbers great enough to detect statistically significant differences in drug effects. So how can researchers avoid making such statistical errors in the analysis of clinical trial data? One way is to include enough women to have a sample size with enough power to be able to detect statistically significant sex differences. Trials this size, however, are generally cost-prohibitive. Industry experts fear that escalating costs for clinical trials will have the effect of stalling medical research, as private companies will not be able to recoup research and development costs.

But there are alternatives to large, costly trials. Dr. Carl Peck of Georgetown University recently proposed a method for conducting Phase I clinical trials in a manner that is both ethical and cost efficient. Safety and dosing information is determined in Phase I trials. These early trials generally have a small sample size (between ten and twenty subjects) and are usually conducted on men. Peck proposes testing an investigational drug first in a small number of men and then testing it in a smaller number of women to determine if the women’s results vary from those of the men. Using Bayesian analysis methods to compare the distribution of these results, one could then determine if the females’ distribution of drug responses differed from that of the males. If it did, then one would need to conduct a separate study in women to determine appropriate dosing and efficacy data. If their distributions were the same, one could then proceed to Phase II trials under the assumption that there were no sex differences in the metabolism of the drug.

Innovative approaches to statistical analysis such as this can pave the

98. See Peck, supra note 66; Pentikis, supra note 63; discussion infra Section II.D.
99. See Peck, supra note 66.
101. See Peck, supra note 66.
103. See Hollan, supra note 103, at 26.
way for drug sponsors to conduct clinical research that is relevant to women, without significantly increasing drug development costs.\footnote{104}{See Peck, \textit{supra} note 66.} Action, however, must also be taken in order to ensure that once sex differences are detected, information about these differences makes its way into drug labeling. It is easier to market a drug that has a one-size-fits-all dosing regimen.\footnote{105}{\textit{Id.}} Currently, there are very few incentives, and no requirements, for drug companies to have different dosing regimens or patient information sheets for men and women. Even when pharmacokinetic and safety data are available, the FDA does not require this information to be included in product labeling.\footnote{106}{B. Evelyn et al., \textit{Women's Participation in Clinical Trials and Gender Related Labeling: A Review of New Molecular Entities Approved 1995-1999} (2001), \textit{available at} http://www.fda.gov/cder/reports/womens_health/women_clin_trials.html (last visited Mar. 24, 2003).}

A recent study by the FDA demonstrates the pressing nature of the drug labeling problem. The study examined the labeling for new drugs approved between 1995 and 1999. Of the 185 product labels analyzed for this study, twenty-two percent of the labels stated that there were sex differences for the drug. Ten percent stated that no studies were performed, studies were inadequate, retrospective review showed no differences, or that the product was not indicated in a specific gender. Thirty-two percent of the labels had no statements about sex.\footnote{107}{\textit{Id.} at 11.} Of the forty-one products for which the labels did describe sex differences, most (ninety percent) were pharmacokinetic. Twelve percent were safety differences and five percent were related to efficacy.\footnote{108}{\textit{Id.} at 13.} Of all 185 products reviewed, not one reported a change in dosage based on sex differences—despite the fact that thirty-seven of these products had known sex differences in their PK properties.\footnote{109}{\textit{Id.}}

\textit{F. Pharmacogenomics.}

Learning more about sex differences is just one step toward improving health care for both men and women. The sex of a patient may soon become a critical piece of information used by clinicians in deciding which antidepressant, cardiac drug, or painkiller to prescribe.\footnote{110}{Deborah Gesensway, \textit{Reasons for Sex-Specific and Gender-Specific Study of Health Topics}, 111:2 (2003).} These exciting

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104. See Peck, \textit{supra} note 66.
105. \textit{Id.}
107. \textit{Id.} at 11.
109. \textit{Id.}
Sex & Gender in Medical Research

Discoveries are the building blocks for even greater advances in the field of medicine. The nascent field of pharmacogenomics, the science of examining the inherited variations in genes and how these variations can be used to predict an individual's response to a drug, holds the promise of allowing clinicians to tailor drug therapies to the individual patient, not just to women or men. Advances in the field have led to new approaches to treating disorders common in women, such as heart disease and breast cancer.

Pharmacogenomics may also reduce the incidence of adverse drug reactions (ADRs) in both women and men. Some of these ADRs could be prevented by changing prescribing practices for patients with a known genetic mutation that negatively impacts treatment outcomes. For women, pharmacogenomics holds the promise of reducing the incidence of cerebral-vein thrombosis (blood clots), a common ADR associated with the use of oral contraceptives. Studies have shown that women who have the G20210A mutation for the prothrombin gene have ten times the risk of developing a blood clot as do women who do not have this mutation. For all women, taking oral contraceptives increases the risk of developing a blood clot by a factor of approximately twenty. It has now been shown that, in women who take oral contraceptives and have the prothrombin mutation, the relative risk of thrombosis is increased to nearly 150. In the future, physicians may screen women for this and other genetic mutations before they are prescribed oral contraceptives. Women with susceptible genetic mutations would then have the option of using other contraceptive and therapeutic regimens. This is just one example of how pharmacogenomics may be used to improve the health of women. As the field matures, pharmacogenomics will offer the opportunity to better understand the pathogenesis of diseases and to improve sub-optimal drug

115. Id.
therapies for each sex.  

III. CONCLUSION

As the nascent field of pharmacogenomics demonstrates, and the 2001 IOM report confirms, it is crucial for researchers to look for differences in their study populations—whether they are differences related to gender or differences between individuals. However, researchers will not be able to detect these differences if study populations do not include appropriate numbers of women and men of all ages and ethnicities.

The inclusion of women in clinical trials has been a major force in the advancement of biomedical research. Paternalistic policies of the 1960s and 1970s gave way under pressure from the burgeoning women's health movement, which instigated landmark reports by the U.S. Public Health Service117 and the United States General Accounting Office.118 These reports led to changes in regulations regarding the inclusion of women in federally funded research.119 As a result, by the late 1990s, record numbers of women were participating in medical studies. The data from these studies has finally resulted in the male norm of medical research being dislodged. Investigators have come to realize that recruiting and retaining women in research studies requires special attention to the unique needs of women. The IOM has recognized the field of sex-based biology as a valid scientific field of study.120 Experts are urging the pharmaceutical industry to collect pharmacokinetic and pharmacodynamic data for women as well as men.121 Statisticians and researchers are investigating novel methods for conducting sex analysis of research data without bankrupting the system with unwieldy study sizes.122

Despite these advances, many issues remain regarding the inclusion of women in clinical trials. Investigators still grapple with ethical issues regarding paternal consent and the inclusion of pregnant women in clinical trials. Even when it is collected, information about important sex

118. See Hearing, supra note 16.
120. See EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH, supra note 49.
121. See Hollan, supra note 108.
122. See Peck, supra note 66.
differences often does not make its way into drug labeling or into the medical literature. There are signs, however, that this is changing. The FDA is proposing major revisions in the format of the content of package inserts to include information about sex differences, and several prominent journals have begun requiring authors to include sex analysis in their manuscripts. The *Journal of the National Cancer Institute (JNCI)* specifically states in its information for authors that “Where appropriate, clinical and epidemiologic studies should be analyzed to see if there is an effect of sex or any of the major ethnic groups. If there is no effect, it should be so stated in Results.”

The wording of the editorial policy of the *JNCI* is particularly noteworthy because it specifically states that negative results must be reported. This is the antithesis of the more common practice of suppressing negative results. It should be noted that several studies have found that publication bias (failure to publish negative findings) is initiated by the investigator and is not due to editorial decisions. The authors found that most unpublished negative findings remained so because the investigators thought the results were uninteresting or they did not have enough time to publish them. By requiring investigators to include sex analysis results, even negative ones, in their manuscripts, journals such as *JNCI* are reinforcing the message of the 2001 IOM report: Sex does matter.

In the past fifteen years, women have made great strides in their participation in clinical trials. As the barriers to appropriate representation

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123. See *Evelyn*, supra note 109.
124. See *Vidaver*, supra note 52.
of women in medical research are being removed and more women volunteer for medical studies, scientists are discovering important sex differences that may lead to improved therapies and prevention strategies for both men and women. More importantly, the greater inclusion of women in clinical trails has led to more equitable research practices and has begun to narrow the information gap regarding women’s health.
Figure 1. Examples of Sex Differences Beyond the Reproductive System.

Differences in Immune Function:

Females have a more aggressive immune response to infectious challenges, but are also more likely than males to develop autoimmune diseases.

Differences in Symptoms, Type and Onset of Cardiovascular Disease:

Men experience heart attacks, on average, 10 years earlier and have a better early survival rate than women. Symptoms of heart attack are also different in men and women. Women more often experience shortness of breath, fatigue, and nausea, while men more often experience crushing chest pain.

Differences in Response to Toxins:

Women are at 1.2- to 1.7-fold higher risk than men for all major types of lung cancer at every level of exposure to cigarette smoke.

Differences in Brain Organization:

Men rely on the inferior frontal gyrus to carry out language tasks. Women use both the left and right inferior gyrus to carry out the same task. Both men and women perform the task equally accurately and rapidly.

Adapted from “Box 1-2: Examples of Sex Difference Beyond the Reproductive System” in Wizemann, supra note 53 at 22-23.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Type of Drug</th>
<th>Primary Health Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescription Drugs With Evidence of Greater Health Risks in Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seldane (terfenadine)</td>
<td>Antihistamine</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Posicor (mibebradil dihydrochloride)</td>
<td>Cardiovascular</td>
<td>Lowered heart rate in elderly women and adverse interactions with 26 other drugs</td>
</tr>
<tr>
<td>Hismanal (astemizole)</td>
<td>Antihistamine</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Propulsid (cisparide monohydrate)</td>
<td>Gastrointestinal</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td><strong>Drugs Prescribed with Equal Frequency to Men and Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raxar (grepafloxacin hydrochloride)</td>
<td>Antibiotic</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Duract (bromfenac sodium)</td>
<td>Analgesic and anesthetic</td>
<td>Liver failure</td>
</tr>
</tbody>
</table>

**Prescription Drugs Without Evidence of Greater Health Risks for Women**