Women’s participation in clinical trials is essential. Factors such as age and weight affect drug metabolism; it is inaccurate to assume that female-specific factors—hormones, percentage of body fat, menstrual cycle changes, and other less tangible influences—have no impact on drug efficacy.

Women, however, have historically been underrepresented in medical research cohorts and clinical studies, including several major myocardial infarction and hypertension treatment trials of the past 10 years. AIDS research has maintained this gender imbalance: men have been the focus of epidemiologic and natural history studies as well as of clinical drug trials for the treatment of HIV infection and its associated opportunistic infections. Until recently, published research has focused on women only as vectors of infection to children and sexual partners, despite the fact that the percentage of women with AIDS has increased steadily from 6.6 percent in 1985 to 11.5 percent in 1990.1 Fortunately, this situation is changing as a result of publicity and political pressure about the inequity and the realization that women are an important pool of potential research subjects.

Women with HIV disease have much to gain from participation in clinical trials. The most obvious advantage is access to the latest medical treatments. Trials also offer concrete psychological advantages. Participants often feel they are maximizing their involvement in controlling the disease and gain personal satisfaction from helping to discover an effective treatment. Because research staff often become involved in education and support, they establish an important caring relationship with participants. Patients frequently experience reduced anxiety as they broaden their network of providers and discover that they are valued and important to study staff.

This article examines the barriers to women’s participation in clinical trials and outlines strategies for medical and mental health practitioners, as well as researchers, to increase this participation.

Barriers to Trial Participation

Barriers to women’s participation in research are both blatant and subtle. They exist on societal, institutional and personal levels.

Societal Barriers. Overt sexism allows researchers to minimize women’s participation with the contradictory justifications that research done on men can be generalized to women, and concern that hormonal differences in women will alter statistical analysis.2 Concerns about women becoming pregnant during the course of a clinical drug trial, the potential of harm to a developing fetus, and resulting liability have led to the exclusion of all women of child-bearing potential from some studies.3 However, the National Institutes of Health (NIH), which provides funding for many HIV epidemiologic studies and drug efficacy trials, is strongly enforcing its regulations for inclusion of women (and minorities). Compliance with these regulations is now a part of the review process for the funding of all NIH grants and contracts.

Covert sexism leads to the situation reported at the 1991 International Conference on AIDS by researcher Deborah Cotton.4 Cotton found that, in addition to geographic variations in the number of women enrolled in HIV clinical trials, the presence of a female principal investigator or coinvestigator resulted in an increase in
The small numbers of women involved in HIV-related clinical trials compromises the care of this growing population of HIV-infected people. Appropriate care for women in the future requires their involvement in clinical trials today. It is the effects of clinical trials on current clients, however, that may be most important to providers.

As Patricia Kelly points out in her article in this month’s FOCUS, clinical trials provide women access to quality health care, expensive treatments, and psychological support. Her overview of the barriers and strategies to recruit women can help clarify the role of mental health and medical providers in this process. More importantly, it can help providers communicate to their clients and patients how to evaluate specific trials, not in terms of treatment protocols but with regard to the psychosocial support they should offer.

Kelly’s perspective is complemented by Terry McGovern’s examination of the legal aspects of the exclusion of women from trials. She portrays a world of so-called facts backed up with little evidence and supported by poor enforcement of government regulations.

It is rare for me to highlight Recent Reports in this editorial. But, this month we focus on two commentaries recently published in the New England Journal of Medicine. These articles look at federal regulations requiring all clinical trials to study subpopulations, including women and people of color. FOCUS is not able to do justice to the complexity of these articles, but I urge readers to consult them for a clarification of the basic scientific and statistical issues at stake.

The issue as a whole provides a comprehensive view of a topic that is not often discussed in therapy. Providers should not dismiss this topic as removed from the treatment challenges that face most clients. Clinical trials continue to be a critical source of care, particularly for women who are less likely to have insurance that will finance their health care.

Getting past discrimination, bureaucracy, and the real complications of performing statistically valid medical research is a challenge not to be understated. But, overcoming the challenge, or even attempting to overcome it, may foster a sense of power and competence.

Whether they confront administrators of specific clinical trials, advocate through their doctors, local researchers, or the FDA, or question insupportable assertions in the courtroom, women may find more than frustration when they seek inclusion in clinical trials. Physicians and counselors must be prepared to help them face frustration and reap the rewards of asserting their rights.

As researchers may decide that they want to enter women into clinical trial cohorts, they often are unaware of the necessity to design and implement recruitment strategies that will attract women. Failure to utilize strategies such as meaningful incentives, child care, or patient-centered scheduling (making appointments available at times convenient for patients as well as providers) means that logistical factors remain as barriers.

The complex structures of some protocols can create a further disincentive for participation. Multiple study questions, rigid eligibility criteria, lengthy questionnaires and examinations, multi-tube phlebotomy, and inflexible clinic hours can be daunting for the most motivated of patients. Women with limited time, symptomatic HIV disease, or young children will be particularly discouraged.

Personal Barriers. Women may not want to participate in research studies. As they are likely to be primary caretakers for all family members, concrete issues such as scheduling, child care and transportation are real impediments to study participation. Inner-city women may not perceive study participation as providing any benefits for themselves, their families or their community. Cultural beliefs may run counter to vigorous medical interventions in a disease process. Women who are active drug users are generally unable to participate until their addiction is under control. Many people of color in the
United States have a justifiable distrust of medical experimentation as a result of the legacy of the Tuskegee syphilis study, and due to abuses in contraceptive studies and sterilization procedures.

**Strategies for Recruiting Women**

The idea of a woman-centered approach can be a guiding principle for what will work to increase women's participation in HIV-related trials. Studies that have used this approach have successfully recruited women who are ethnic minorities, immigrants, drug users, or people from lower socio-economic backgrounds.

Responsibility for recruitment is shared by both field staff and investigators. While field staff must identify subjects and discuss study participation with them, it is the responsibility of investigators to provide the resources for such work. Field staff often feel pressured to meet unrealistic recruitment goals, in populations difficult to recruit into research protocols, without having the necessary tools to complete the job. To do so, investigators must provide patient incentives, time, and office or clinic space.

Successful recruitment activities are facilitated by an effective organizational framework. This might mean that one staff member has overall responsibility for coordinating and assessing the success or failure of different recruitment strategies. It might also involve using a database-based management system, which allows rapid, objective feedback about performance that can be shared with other staff at regular meetings.

Essential to the task of successful recruitment of women into clinical trials is a non-judgmental, supportive staff. Drawing field staff from the community of the desired study population further facilitates recruitment. Bonds of trust result more easily when language and culture are shared, especially when addressing the historic suspicion of research participation. Staff can create a caring environment by welcoming participants in an open, non-judgmental manner, both at the time of their scheduled study visits and when they have physical or emotional needs. Study staff frequently report that one of the most important reasons that women enter clinical trials, and one that is often unacknowledged, is the ability of staff to take extra time with study participants and provide them with education and counseling about their HIV disease. If sufficient trained staff are available, rotating a beeper for 24 hour on-call telephone coverage lets study participants know that someone will be available to them.

Staff forums can provide the support and supervision necessary for staff who go to such lengths to recruit women and meet their needs. Regular discussion about roles, overidentification, limit setting, and emotional issues raised by their work can prevent staff burnout and maximize effective relationships with study participants.

**Incentives**

Integration of clinical care into the research setting is a definite enhancement for research participation. It is important to attend to aspects of clinical care during study visits or to try to complete all or part of the study protocol during a regularly scheduled clinic visit. An organized system that makes research test results available to clinicians (with signed consent from patients) avoids unnecessary replication of costly laboratory tests for agencies and multiple venipunctures for patients. A drug treatment counselor available for emergency situations and ongoing counseling, regularly scheduled psychological support groups, and acupuncture or other complementary therapies all enhance clinical care and study recruitment.

Mental health staff can work together with study staff to ensure that women research participants have their medical and psychological needs met. These link-

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**References**

ages are especially important when research studies end and study staff terminate their relationships with participants. In such cases mental health staff may be asked to address patient needs that had been previously met by researchers or to work with participants who feel abandoned or resentful about termination.

Investigators and administrators can encourage participation by creating a positive clinic environment and offering meaningful incentives to subjects. The clinic environment can promote or discourage recruitment. Administrators can create a welcoming environment by providing a comfortable, congenial space for patient visits; making literature, videos, and coffee, tea, and snacks freely available; and encouraging a positive staff attitude. Depending on the number of patients seen, researchers might make available a volunteer or staff member to provide child care, or prepare a secure, defined play area equipped with easily cleaned toys. In order to allow patients to get in and out with a minimum of waiting time, bother, and paperwork, researchers should ensure that there is flexibility in terms of staff and clinical times.

Incentives such as transportation stipends, paid in cash at the time of every study visit, are essential. Other incentives make study participation easier for subjects and provide them with a small but concrete return. Some groups have given T-shirts, mugs, baby clothes, diapers, baby pictures, or tote bags, varying these by visit. In prospective studies, where there is a greater investment over time, it is a good idea to make the incentives more attractive with study longevity. An annual holiday party or summer outing can provide a welcome break for study participants, their families, and staff. Staff can easily maintain a system for sending birthday and holiday cards by using a computerized data base.

Even with an open environment, it is important to maintain patient confidentiality. HIV-related brochures should be displayed only with other health-related literature, questions from casual passers-by or patient family and friends—“What kind of clinic is this?” or “What kind of research do you do here?”—answered in general terms, and HIV-related information about specific patients discussed only with those whom the patient has specified in a written consent. Birthday cards and other mailings to study participants should omit mention of “AIDS” or “HIV.” In addition, not every staff member in a multi-service agency needs to know that clients are coming in to participate in an HIV clinical trial.

**Conclusion**

Ensuring that women with HIV disease have knowledge about and access to clinical trials is important. Mental health providers can assist women to enroll in research studies by initiating discussion about available clinical trials, answering questions, and clarifying confusing details and technical concepts (for example, “double-blind” and “placebo”).

By maintaining communication with research staff, having a general idea of available studies, and knowing what psychological and concrete incentives are offered, mental health staff can provide a realistic picture of the advantages and disadvantages of study participation. Their most important contribution to the enrollment of more women is to facilitate non-coercive discussion during which women with HIV disease can work through the decision-making process about study participation.

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**Clearinghouse: Women and Trials**

**References**

Allen MH, Marte C. HIV infection in women: Presentations and protocols. *Hospital Practice*. March 15, 1992; 113-120.


Nuckols T. Pregnancy and HIV infection.
HIV-infected women are often unable to gain access to the early phases of clinical trials. There are numerous obstacles at work, some of which have to do with the U.S. Federal Drug Administration’s (FDA) guidelines on the subject and the specific inclusion and exclusion criteria of a given protocol. Other obstacles relate to the general lack of health care and treatment options many HIV-infected women face. This article outlines federal regulations on the inclusion of women in clinical trials and describes the response of pharmaceutical companies to these regulations.

An example: A physician recommended that one of his patients participate in Phase I of the Johns Hopkins University/Hoffmann-LaRoche tat-inhibitor clinical trial. The protocol’s first inclusion criterion was: “Male or female of non-childbearing potential (surgically sterile, one year postmenopausal).” When one woman attempted to enroll in this phase, trial administrators told her that she would have to be surgically sterilized.

The client was willing to undergo pregnancy tests, use detectable birth control, and sign a waiver and covenant not to sue. She was not, however, willing to undergo surgical sterilization. Even with the HIV Law Project’s intervention, trial administrators prevented her from enrolling in Phase I of the trial. The question is why. It seems that what lies at the heart of the controversy is the fear of drug companies that they will incur huge liability costs by allowing women into trials.

Since the 1970s, which saw successful litigation in cases involving the drugs DES and thalidomide, pharmaceutical companies have been extremely cautious about allowing women into clinical trials. Although a statement releasing the manufacturer from liability is generally included in the informed consent agreement,
ties, children and hemophiliacs, are to be included in clinical research.\(^1\) On the other hand, the federal regulations severely limit research on pregnant women or fetuses.\(^2\) For example, FDA guidelines for the clinical evaluation of drugs recommend that women of childbearing potential should be excluded from clinical trials until FDA animal reproduction guidelines have been completed, except in the case of life-threatening illness. The National Institutes of Health (NIH) has recently established policies and procedures designed to enroll more women and people of color in HIV-related clinical trials:\(^3\)

Unfortunately, these policies apply only to AIDS Clinical Trials Group (ACTG) studies and not to studies initiated by private drug companies.

In summary, where a drug is intended to address the effects of a life-threatening disease (including HIV infection), men and women who have that disease may participate in the drug trial regardless of the outcome of animal reproduction studies, provided that researchers fully explain the results and implications of these studies and treatment alternatives.

**Scientific Rationale**

Although the FDA guidelines appear to be straightforward, drug companies continue to use more restrictive policies. For example, the woman who wanted to join the tat-inhibitor trial was still denied entry. Hoffmann-LaRoche explained that it had not yet finished animal reproduction studies and therefore was excluding women. Under the FDA guidelines, however, she should have been included since she suffers from a life-threatening illness.

According to at least one pharmacologist aware of the clinical trial, the tat-inhibitor is a diazepine derivative, a class of drugs that has been well-studied by Hoffmann-LaRoche prior to its application to HIV infection. These studies show no evidence of long-term negative effects on women’s reproductive systems. Moreover, if, despite these studies, the drug was thought to be capable of inflicting long-term damage upon the reproductive system, then men might also risk such damage. Yet there is no requirement that men participating in the trial be surgically sterilized.

Further, while the Investigational New Drug (IND) application process mandates that trial sponsors report on efficacy and toxicity, there is no requirement that they report on or even file with the IND application, the results of animal reproduction studies, or any evidence of fetal toxicity. As a direct result of the FDA’s failure to monitor these results and the application process, trial sponsors have been able to exclude women on the basis of fetal toxicity when in fact there is no evidence of such toxicity. Thus, the animal studies which the FDA requires as a precursor to women’s participation in clinical trials may never be conducted or may be conducted parallel to, not in advance of, clinical trials.

The FDA has recently announced that it is rescinding the discriminatory 1977 guideline, which restricts the access of women of childbearing potential to the early phases of clinical trials. Instead, it leaves this decision to the discretion of trial sponsors. The FDA does not propose, however, any regulatory changes that would require the completion of animal reproduction studies prior to human testing. It remains unclear whether the use of gender-discriminating protocol criteria will cease, especially since the FDA does not actively monitor the process.

**Conclusion**

Without studies proving danger to women’s reproduction, the current drug development process results in women using approved drugs that have not been adequately tested for them, and it denies many women the health care available only through drug trials. The failure of pharmaceutical companies to follow FDA guidelines and the failure of the FDA to enforce these guidelines means that women will continue to suffer discrimination related to clinical trials. To battle this discrimination and deliver appropriate treatment to women, health providers as well as activists—and men as well as women—must challenge drug company phobia regarding liability and FDA reticence regarding enforcement.

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\(^1\) Additionally, for all trials conducted through the AIDS Clinical Trial Group system, NIH policy requires that a compelling scientific rationale be submitted for any trial that does not include women. See “NIH/ADAMHA Policy Concerning Inclusion of Women in Study Populations,” NIH Guide for Grants and Contracts. (First published October 24, 1986, most recently published February 8, 1991.) Similar policy has been issued that seeks to redress the absence of people of color in clinical trials.

**References**

2. 42 USC 300cc-16.

**Authors**

Terry McGovern, JD is Director of the HIV Law Project, which provides legal services to HIV-infected people living in New York.

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**Women and HIV Conference**

The Second Annual Women and HIV Conference will be held on Saturday, October 23 at the University of California Irvine Student Center. Conference admission is $10 for full-time students, $15 for the general public, and $30 for health care professionals. To register, or for further information, phone South Coast Medical Center at 714-499-7205.
**Two Perspectives on Women in Trials**


In response to proposed National Institute of Health (NIH) and Food and Drug Administration (FDA) guidelines for all clinical trials (including HIV-related ones), two commentaries examine the effects of the underrepresentation of subgroups in medical research.

The first focuses on possible consequences of mandatory inclusion of underrepresented groups in clinical trials and emphasizes the statistical challenges of studying subgroups. Despite the validity of arguments to include women in research samples, statistical considerations require factoring the biological plausibility of sex-related differences with the time and money needed to pursue meaningful research. Nonetheless, cost should not be a consideration in determining whether to include members of subgroups in trials.

In designing a study, researchers must balance conflicting desires between the homogeneity and heterogeneity of a study cohort. The study cohort must be homogeneous enough to yield a low level of variability and diverse enough to allow any findings to be generalizable beyond narrow subgroups. To achieve these ends, a common strategy is to gather cohorts that mirror the composition of the general population that would receive the treatment. But clinical trials are rarely large enough to test reliably the treatment effect within subgroups, and extremely large samples may be needed to detect significant differences among subgroups. The high cost and complexity of large-group trials, however, prohibit their development except in the cases of the most common diseases.

In conclusion, when researchers exclude women entirely, they cannot gain even a hint about differential response. Merely including some women, however, is not sufficient to learn how to treat women, and even including women in the same proportion as they appear in disease prevalence statistics may not provide reliable information.

The second article concentrates on reasons why formal guidelines are needed to ensure that the effects of drugs on women are specifically studied. Despite the fact that many trials have included large numbers of women, a 1988 General Accounting Office study found that only about half contained analyses of data related to subgroups.

The new FDA guidelines urge the inclusion of “reasonable numbers” of women in clinical trials. This is important because of pharmacokinetic (the concentration of a drug in the blood or other tissue over time) and pharmacodynamic (the body's response to a given concentration of a drug) differences between men and women.

These differences are related primarily to variations in body size and composition and the effects of hormones. Four hormonal factors seem to be relevant: the levels of gonadotrophins and circulating steroidal hormones during menstruation; the differences between pre- and postmenopausal women, including those who receive hormone-replacement therapy; the drastically different hormone levels during pregnancy and the metabolic consequences of pregnancy; and the relationship between steroidal contraceptives and metabolism of drugs in terms of drug and contraceptive efficacy.

The article calls for inclusion of women with childbearing potential in all phases of clinical trials. It states that women have the ethical right to make personal choices about participation and notes that it is possible to design protocols to reduce fetal exposure to drugs.

**Psychological Effects of Clinical Trials**


Participation in a clinical trial for zidovudine (ZDV; AZT) did not have any adverse psychological effects on asymptomatic HIV-infected subjects, according to a small Minneapolis study. In fact, participation may have actually reduced factors that lead to stress, anxiety, and depression.

Forty-six study subjects and 27 control subjects completed a questionnaire consisting of several standardized psychological surveys when they entered the trial;

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**Recent Reports**

Clinical trial participants reported significantly lower levels of stress, anxiety, and depression than people who did not participate.
after two months, and after six months. The surveys were designed to measure levels of hopelessness, anxiety, depression, and well-being. All but one of the subjects was male, and their average age was 34.

Study subjects reported significantly lower levels of stress, anxiety, and depression at the end of the six-month period. Control subjects also reported a decrease in depression, but no significant change in stress or anxiety. Subjects who had clinically high levels of stress, anxiety, and depression prior to the study reported no significant changes during this period. Researchers attributed beneficial effects to feelings of altruism and emotional support gained through participation in the clinical trial.

HIV in Pregnant Women


A survey of obstetricians at AIDS clinical trials centers around the United States established a bank of knowledge about the clinical and immunologic status of HIV-infected women and found that new strategies are needed to care for these women and combat the progress of their illness.

Forty-five obstetricians from the 49 federally supported AIDS clinical trials centers provided information about the health of HIV-infected pregnant women under their care. They estimated that 1,000 to 1,800 HIV-infected women had given birth at these centers during the year prior to December 1989. Eighty-two percent of these women were asymptomatic, 12 percent were symptomatic, and 6 percent had AIDS. While 43 of the centers (96 percent) had established formal prenatal HIV antibody testing, only 30 (67 percent) performed T-helper cell testing as a standard procedure. Seventy-six percent of the physicians had referred a patient to an AIDS clinical trial.

Among subjects who were symptomatic or who had AIDS, 35 women had *Pneumocystis carinii* pneumonia (PCP), the most common illness reported, 17 had active tuberculosis, and 15 had candidiasis. Fifty women had sexually transmitted diseases associated with ulcers. Zidovudine (ZDV; AZT) was the most commonly used AIDS drug but was administered to only 29 women, since its safety during pregnancy is still being evaluated. PCP prophylaxis—which is not recommended for pregnant women—was used in only 40 cases. The authors suggest that more routine T-helper cell testing could identify those pregnant women for whom PCP prophylaxis might be warranted.

Minority Recruitment for Clinical Trials

El-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *Journal of the American Medical Association.* 1992; 267(7): 954-957. (Harlem Hospital Center and Columbia University.)

A commentary on minority recruitment for AIDS clinical trials suggests that strategies to increase participation must respond to the lack of social and educational support services available to minority participants and to their historical distrust of the process of medical research.

An analysis of past AIDS trials reveals a consistent trend of low minority enrollment. African Americans and Hispanics have constituted between 18 and 35 percent of the population in zidovudine (ZDV; AZT) efficacy studies, despite the fact that they make up 45 percent of reported AIDS cases. Minorities have also been underrepresented in studies of the natural history of HIV. Because of the inability of researchers to draw statistical conclusions from small samples of minority participants, these studies have led to inconclusive results about the effectiveness of ZDV in this population.

Next Month

Family interactions can confound an already complicated psychosocial situation for people with HIV disease. In families that are poor and where more than one family member may be infected, these dynamics are all the more confusing. In the November issue of FOCUS, Robert Tufel, MSW, MPH, Program Director of Family Special Services, and Geri Brooks, PhD, Executive Director of Sunburst Projects, both in San Francisco, outline the psychosocial issues poor, HIV-affected families face and the impact these issues have on family dynamics.

Psychotherapy may be useful to help families deal with the stresses of HIV disease. Also in the November issue, Gillian Walker, MSW, Co-Director of the AIDS and Families Project of the Ackerman Institute in New York, discusses approaches to family therapy for poor, HIV-affected families.
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