Guidance - Women as Subjects in Research

Presents requirements for the participation of women with child-bearing potential in research trials, including clinical trials.

Introduction

Historically, there have been concerns about the participation of women with child-bearing potential in research trials due to potential risks of fetal harm should a woman become pregnant. Such apprehension has resulted in guidelines or policies from Federal agencies that called for special protection for women.

Over the past decade, questions have been raised by professional, consumer, and governmental groups about whether clinical treatments are adequately tested in various populations that are the recipients of such therapies. In terms of drug development, the FDA began to consider information available pertaining to the safety and effectiveness of drugs for women and subpopulations such as the elderly and diverse racial groups. In 1988, the Agency issued a guideline that called for safety and efficacy profiles for these groups as part of new drug applications (NDAs). (FDA Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications, 1988). Then in 1993, following broad public discussion about participation of women in clinical trials, FDA issued a new guideline that eliminated the restriction on participation of women with childbearing potential from all phases of drug trials. It detailed procedures to minimize the risks of pregnancy in women participants such as contraceptive counseling, pregnancy tests, timing of short term studies in relation to the menstrual cycle, and the process of informed consent.

The guideline underscored that while FDA remained involved in general risk/benefit determinations for subjects entering various phases of clinical trials, initial determinations about whether fetal risk is adequately addressed are properly left to patients, physicians, local IRBs, and study sponsors. The new guideline also called for gender analyses with special attention to factors affecting pharmacokinetics, e.g. the role of the menstrual cycle and exogenous hormone therapy in relation to the drug, as well as the influence of the drug on oral contraceptives.

The NIH has also examined carefully the issue of participation of women in research. It has determined that since the primary aim of biomedical and behavioral research is to provide scientific evidence leading to a change in health policy or a standard of care, it is imperative to determine if the intervention or therapy being studied affects men and women differently.

The agency has concluded that the inclusion of women in research is sufficiently important that the only justifiable reason to exclude women of child-bearing potential from federally funded research is compelling evidence that the proposed project would be inappropriate with respect to the health of the subject or the purpose of the research. *(Federal Register, Vol. 58, No. 139, p 39406 -39416, H, Thursday, July 22, 1993* and *NIH Guidelines On The Inclusion of Women and Minorities as Subjects in Clinical Research. NIH Guide, Vol. 23, No. 11, 3/18/94*.)

The following statement pertains primarily to the inclusion of women as subjects in clinical trials, i.e., medical research. However, the inclusion of women in behavioral research studies is also

important and must be accomplished unless there is a compelling rationale which establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Significant portions of the text below are presented verbatim as published in the Code of Federal Regulations and the Federal Register.

Geisinger endorses these changes and has adopted the following regarding the inclusion of women as subjects in human research as a guideline to researchers.

Pregnant Women as Human Research Subjects

Drug research using pregnant women as subjects is governed by federal regulations. Geisinger considers it prudent to apply these requirements to clinical research involving pregnant women, as follows:

> *"No pregnant woman may be involved as a subject in a human clinical research project unless (1) the purpose of the research is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal. {Research involving the use of pregnant women as subjects} may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if (1) the purpose of the research is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape." (45 CFR 46.207)*

Women of Childbearing Potential as Human Research Subjects

Women **should not** be excluded from any phase of research unless the science of the project or the health of the subject will be compromised. Regarding clinical drug research, Phase I, II, and III trials should have the proportion of women in the study which at least reflects the proportion of women in the population which will receive the drug when it is marketed, and should enroll numbers adequate to detect clinically significant sex differences in drug metabolism and response.

Risk to Fertility

It is expected that experimental subjects will be informed about potential risks to their fertility including the development of any abnormalities or abnormalities in function of reproductive organs as a consequence of the proposed study intervention.

> ***"Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals as a consequence of the proposed study intervention, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative treatment and the duration of therapy.***

Where [women] of reproductive potential are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate monitoring and/or laboratory studies to allow detection of these effects. Long-term follow-up will usually be needed to evaluate the effects of such drugs in humans." (Federal Register, Vol. 58, No. 139, p 39411, H, Thursday, July 22, 1993.)

Risk to Fetus and/or Infant

General Guidelines:

"Appropriate precautions should be taken in research studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and patients of potential risk and the need for precautions. In all cases, the informed consent document and investigator's [drug information] brochure should include all available information regarding the potential risk of fetal toxicity. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their significance in humans. If these studies have not been completed, other pertinent information should be provided, such as general assessment of fetal toxicity in drugs with related structures or pharmacological effects. If no relevant information is available, the informed consent should explicitly note the potential for fetal risk. In general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of child-bearing potential, i.e., usually by the end of phase II and before any expanded access program is implemented." (Federal Register, Vol. 58, No. 139, p 39411, G, Thursday, July 22, 1993.)

Minimizing the Possibility of Fetal Exposure

Pregnancy testing may be used to detect unsuspected pregnancy prior to initiation of study treatment. Timing of the start of the study to coincide with or immediately follow the onset of menses is also an adequate indication that the subject is not pregnant. The investigator should ascertain that the subjects will responsibly employ a reliable method of contraception or abstinence for the duration of the drug or treatment exposure, which may exceed the length of the study. If requested, the investigator should be able to refer the subject to a knowledgeable counselor or physician for contraceptive advice.

Inclusion of Women in Early Clinical Trials (Phase I and early Phase II)

"In some cases, there may be a basis for requiring [inclusion] of women in early studies. When the disease under study is serious and affects women, and especially when a promising drug for the disease is being developed and made available rapidly under FDA's accelerated approval or early access procedures, a case can be made for requiring that women [be allowed to] participate in clinical studies at an early stage. When such a drug becomes available under expanded access mechanism (for example, treatment IND or parallel track) or is marketed rapidly under subpart E

procedures (because an effect of survival or irreversible morbidity has been shown in the earliest controlled trials), it is medically important that a representative sample of the entire population likely to receive the drug has been studied, including representatives of both genders. Under these circumstances, clinical protocols should not place unwarranted restrictions of the participation of women." (Federal Register, Vol. 58, No. 139, p 39409, G, Thursday, July 22, 1993.)

Risk to Infant of Nursing Mother

The potential for harm from exposure to a drug with unknown risks exists for nursing infants as well as fetuses. Therefore, this policy applies to breast feeding female subjects who are potential subjects in a drug trial in the same manner in which it applies to gestating women.

Active Recruitment of Women

In order to assure that adequate numbers of women are included, researchers are encouraged to actively recruit women into their trials. For specific outreach methodologies, researchers may obtain the "NIH Outreach Notebook of the Inclusion of Women and Minorities in Biomedical and Behavioral Research."

Sample Informed Consent for a Potentially Toxic Drug Study

The following language is recommended when women of child-bearing potential (non-pregnant) will be enrolled into a potentially toxic drug study:

"If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this drug study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk [or state specific risk].

To confirm to the extent medically possible that you are not pregnant, you agree [to have a pregnancy test done before beginning this research study] [to begin the study after the onset of your next menstrual period] (choose one). You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study."

Protocol Continuing Review

Investigators applying for a continuing review of their research protocols are encouraged to comply with these new guidelines to the extent that the science of their project is not compromised.