

WOMEN OF CHILDBEARING POTENTIAL IN CLINICAL RESEARCH: PERSPECTIVES ON NIH POLICY AND LIABILITY ISSUES

By Eugene G. Hayunga, Karen H. Rothenberg, and Vivian W. Pinn*

I. Introduction

For many years there has been a presumption that women of childbearing age are to be automatically excluded from clinical studies. This approach has led to continued gaps in our scientific knowledge, as important information about metabolic activity and drug interactions in this group of subjects is not readily available. As a result, there is the possibility that drugs may be marketed with undetected side effects, or that the benefit of potential treatments may be delayed for women who may not have access to novel interventions as early in the research process as their male or infertile female counterparts.

In the past government regulations have emphasized the ethical principles of beneficence and respect for persons in protecting subjects from risks and assuring their right NOT to participate in research studies.¹ This has not changed. But we now also recognize the important ethical principle of justice with regard to who receives the benefits of clinical research and in assuring an individual's right TO participate in research. As a result, investigators are now encouraged to use fertile women earlier in clinical trials. Such a change in thinking represents a major landmark.

The new NIH requirements to include women as research subjects reflect the most recent changes in accepted standards of practice. In this article, we describe the experience of the National Institutes of Health (NIH) in developing and implementing its policy regarding the representation of women as research subjects, address the relevance of this policy to women of childbearing potential and pregnant women, and consider the liability implications of their inclusion in research studies.

II. Role of the NIH Office of Research on Women's Health

The Office of Research on Women's Health (ORWH) was established in September 1990 within the Office of the Director, NIH. ORWH serves as a focal point for women's health research at NIH in setting and monitoring policy, promoting and stimulating research, and enhancing scientific career development. ORWH works in partnership with the NIH research institutes, centers, and divisions to ensure that women's health research becomes an integral part of the scientific fabric at NIH and throughout the scientific community. ORWH has a threefold mandate:

- to strengthen and enhance research related to diseases, disorders, and conditions that affect women and to ensure that research conducted and supported by NIH adequately addresses issues regarding women's health;
- to ensure that women are appropriately represented in biomedical and behavioral research studies supported by NIH; and
- to develop opportunities for recruitment, retention, re-entry, and advancement of women in biomedical careers.

III. NIH Policy

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.²

This policy has evolved over the last decade. The Public Health Service assessed the representation of women in clinical trials in 1985,³ and NIH policy has addressed the inclusion of women and minority subjects in clinical research since 1986.⁴ The policy was strengthened in 1990 in response to weaknesses noted in the General Accounting Office (GAO) report of that year.⁵ The NIH Revitalization Act of 1993 (PL 103-43) gave existing policy the force of law⁶ and stipulated some additional requirements, including a proscription against considering costs when evaluating research plans.⁷ The legislation also delineated some general exceptions to policy.⁸

The revised policy applies to all research involving human subjects.⁹ As described in the Guidelines, clinical research is defined broadly because of the need to obtain data about minorities and both genders early in the research process when hypotheses are being formulated, baseline data are being collected, and various measurement instruments and intervention strategies are being developed.¹⁰ Phase III clinical trials are to be designed and carried out in a manner that will provide for valid analysis of whether the variables being studied affect women or members of minority groups differently than other subjects in the trial.¹¹ In all cases, the research study designs are evaluated prospectively by the NIH, as funding is contingent upon a satisfactory

inclusion plan that must meet the requirement before the study may commence.¹²

IV. Implementation of the NIH Policy

One of the first steps in implementing the revised policy was to familiarize the staff of some 23 separate NIH institutes, centers, and divisions with the new requirements. This task was especially critical in light of findings by the General Accounting Office (GAO) in 1990 that the earlier policy had been inconsistently applied and had not been well communicated or understood within NIH or the research community.¹³ Thus, the changes mandated by the Revitalization Act provided an opportunity to reinforce the NIH commitment to inclusion by issuing renewed policy guidance, first to NIH staff and then to the entire scientific research community.¹⁴

The NIH "Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research" were published as a Notice in the *Federal Register* on March 28, 1994 (Guidelines). The Notice described revisions to policy made in response to the Revitalization Act and invited public comments during the first year of implementation.¹⁵ A variety of outreach activities were also initiated to explain the revised policy and to correct common misunderstandings about its requirements. NIH staff gave presentations on the Guidelines at numerous professional meetings and workshops, and NIH published a "Questions and Answers" document to provide more detailed policy guidance and address some of the more commonly asked questions about implementation of the Guidelines.¹⁶

The Guidelines emphasize that the policy is intended to address gaps in scientific knowledge. A clinical study without appropriate numbers of women or minority subjects may be scientifically flawed, as would one without an appropriate control group or one with serious methodological weaknesses. Thus, inclusion should be considered an issue of scientific merit. For this reason, it is the responsibility of peer reviewers to assess a project's inclusion plan as part of their evaluation of the research design. Under NIH review procedures, any application or proposal that is deemed unacceptable with regard to inclusion during initial review receives an administrative bar-to-funding, as does one found to be unacceptable with regard to the safeguarding of human subjects or the use of vertebrate laboratory animals. When this happens, the situation that caused the bar must be corrected before an NIH research institute or center may lift the bar and make an award.¹⁷

V. Women of Childbearing Potential and Pregnant Women

In September, 1992, ORWH commissioned the Institute of Medicine (IOM) to establish a Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies (Committee). The Committee

was charged with examining the ethical and legal implications of policies that would broaden inclusion of women in clinical trials, including women of childbearing potential and pregnant women.¹⁸ The Committee's recommendations were finalized after passage of the Revitalization Act but before publication of the NIH Guidelines. Much of the Committee's recommendations were incorporated to varying degrees into NIH policy; however, the NIH Guidelines do not specifically address special rules for pregnant women.

The Committee recognized the potential benefits of participation in research, such as access to new therapeutic interventions that might otherwise not be available. They emphasized respect for the autonomy of women to make decisions regarding their participation in clinical research studies and recommended that women who participate in research studies should be permitted to select voluntarily the contraceptive method of their choice where there are no relevant study-dependent, scientific reasons for excluding certain contraceptives, such as drug interaction.¹⁹ The Committee recommended that federal policy should assure that neither women nor men of reproductive age should be excluded from participation in clinical studies.²⁰ Both should have the opportunity to participate in the benefits and burdens of research. The potential or prospect of becoming pregnant during a study should not be used as a justification for precluding or limiting the participation of women of reproductive age.²¹ The Committee further recommended that pregnant women should also be presumed eligible for participation in clinical studies.²² At the same time, it is important to note that presuming pregnant women to be eligible is not the equivalent of advocating their active recruitment into every clinical study, as there may be scientifically and medically valid reasons for excluding pregnant women from a particular study.²³

In moving from a paradigm of exclusion to one of inclusion, much still needs to be done to overcome some of the barriers that have prevented women from full participation in the past. For this reason ORWH has made some resources available to assist investigators in their outreach efforts, by providing support through administrative supplements to ongoing NIH grants. In July of 1993, ORWH sponsored public hearings and a workshop entitled "Recruitment and Retention of Women in Clinical Studies," and subsequently published a summary of the issues and recommendations.²⁴ The NIH also published an "Outreach Notebook" that offers some practical suggestions for recruitment and retention of underrepresented subjects.²⁵

VI. Liability Issues

As a result of government policies on inclusion, the standard of practice for conducting clinical research is being changed. It is not entirely clear what effect this will have on future liability claims by women or their offspring who are injured as a result of their participation as

research subjects.²⁶ Liability issues are not addressed in the NIH Guidelines.

Medical researchers and pharmaceutical manufacturers share a fear that if a woman participating in research becomes pregnant and her fetus is harmed, they will be held liable.²⁷ This fear is often the reason for the exclusion of women from clinical trials, despite a very low reported incidence of research injuries and few reported legal cases concerning such injuries.²⁸ Fear of liability has not, however, operated to exclude men from participating in clinical trials, despite evidence that some fetal injury may be attributed to exposure of the father to toxic substances.²⁹ Ironically, fear of liability has never operated as a rationale for the inclusion of women in clinical research, even though there may be more legal precedent for liability for exclusion.³⁰

The informed consent process is critical to assessing liability in research.³¹ Potential liability for injuries to women and men who participate in clinical research is unlikely, provided that informed consent to participate in the research is obtained in accordance with federal regulations and state tort law.³² Liability, then, turns on the "informed" nature of the woman's consent to participate in the research and whether she has been adequately warned about potential risks.³³ If the researcher has met the requisite standard of care by warning the woman of the potential risks of the trial in which she wishes to participate, and she chooses to participate, it is unlikely that she will succeed in any subsequent negligence action for injuries that may occur as a result of her participation in the trial.

Questions of liability more often focus on potential harm to the future offspring of women who participate in clinical trials. It is unclear in this context whether obtaining the informed consent of the mother would be sufficient to avoid liability for the injury to the offspring. The mother's consent would probably suffice when the research is of therapeutic value to the fetus,³⁴ but it is not clear if this would be the case when the drug or intervention was designed to be therapeutic for the mother only.³⁵ To date there has been little case law establishing parameters for holding researchers or drug manufacturers liable for injuries to the offspring of clinical trial participants, but liability has been found when there was failure to obtain consent.³⁶ It appears, then, that when there is no negligence and appropriate informed consent to participation in a clinical trial has been obtained, researchers and sponsors are unlikely to be held liable in tort for the inclusion of women in their studies.³⁷

Unlike speculation about liability for inclusion, legal precedent does exist that has based liability, in part, on the inadequate testing of a drug before it was released into the market.³⁸ The evolution of public policy that establishes the importance of including women in clinical research has prompted several commentators to suggest that researchers and drug manufacturers should focus their concern on liability that results from the exclusion of

women from clinical research.³⁹ Indeed, the thalidomide tragedy, perhaps the most notorious example of injury to offspring following the use of medication during pregnancy, involved a pharmaceutical that had already been marketed and was in widespread use. Thus, it is arguable that the failure to include women of childbearing potential in controlled clinical trials may result in the risk of injury to more individuals in less controlled and less monitored circumstances. It is also possible that a medical malpractice claim could result from the inappropriate application of a treatment regimen that was developed through research in which only men were studied. Thus, in contrast to a research injury which results from being included in research, liability for exclusion results from the lack of data necessary to establish appropriate standards for the treatment of women.

It is also important to note that unforeseen complications and unintended injuries, however tragic they may be, do not necessarily result in legal liability. Nevertheless, conscience compels that something be done to right the wrong. To a certain extent, the scientific community has already accepted responsibility for some adverse outcomes related to clinical research. Research protocols or informed consent documents may provide that if something goes wrong during the course of a study the subject will be treated at no expense. However, such provisions typically do not extend to compensation beyond immediate medical treatment, nor do they address injury to offspring. Clearly, more attention must be given to developing better remedies for potential injuries associated with research activities. These might include the possibility of a "no fault" approach for most research related injuries regardless of liability, while at the same time preserving the option of tort action for negligence.

VII. Conclusion

Questions concerning risk of liability are difficult to resolve, but there is growing consensus that the exclusion of women from research studies may pose just as much risk of liability as their inclusion. Liability for inclusion depends very much on the informed nature of the woman's consent to participate in the research. The actual informed consent document should be viewed as more than just a piece of paper to protect the sponsor. Instead, it is an important indicator demonstrating the quality of interaction that has taken place between investigator and subject throughout the research project.

Perhaps the most cogent argument in favor of the NIH inclusion policy is the societal cost of continued gaps in scientific knowledge about important health problems that affect both women and men of diverse racial-ethnic groups.⁴⁰ Gender differences must be appraised when generalizing results to entire populations,⁴¹ because a "one size fits all" standard of care is no longer acceptable.⁴²

Endnotes

1. U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, D.C. U.S. Government Printing Office, 1978. DHEW. Publication No. (OS) 78-0012. Reprinted in 44 Fed. Reg. 23,192. (April 18, 1979).
2. U.S. Department of Health and Human Services, National Institutes of Health. *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*; Notice. 59 Fed. Reg. 14508-14513 (March 28, 1994) (Guidelines).
3. U.S. Department of Health and Human Services. *Report of the Public Health Service Task Force on Women's Health Issues*. DHHS Publication No. (PHS) 88-50206.
4. LaRosa, J.H., B. Seto, C.E. Caban, and E.G. Hayunga. 1995. Including women and minorities in clinical research. *Applied Clinical Trials* 4(5): 31-38. (May 1995)
5. Nadel, M.V. *National Institutes of Health: Problems in Implementing Policy on Women in Study Populations*. U.S. General Accounting Office. Testimony before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, June 18, 1990.
6. 103-43. *National Institutes of Health Revitalization Act of 1993*, Pub. L. No. 103-43, 107 Stat. '22 (codified at 42 U.S.C. § 289.a-1).
7. As described in the 1994 Guidelines (*supra*, note 2), "The new policy requires that, in addition to the continuing inclusion of women and members of minority groups in all NIH-supported biomedical and behavioral research involving human subjects, the NIH must:
 - Ensure that women and members of minorities and their subpopulations are included in all human subject research;
 - For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished;
 - Not allow cost as an acceptable reason for excluding these groups; and,
 - Initiate programs and support for outreach efforts to recruit these groups into clinical studies."
8. The Guidelines (*supra*, note 3) repeat the language of PL 103-43, (*supra* note 6), to explain that, "Exclusions to the requirement for inclusion of women and minorities are stated in the statute as follows:

The requirements established regarding women and members of minority groups shall not apply to the project of clinical research if the inclusion, as subjects in the project, of women and members of minority groups, respectively—

 - (1) Is inappropriate with respect to the health of the subjects;
 - (2) Is inappropriate with respect to the purpose of the research; or
 - (3) Is inappropriate under such other circumstances as the Director of NIH may designate." 492B(b); and

"(B) In the case of a clinical trial, the Guidelines may provide that such inclusion in the trial is not required if there is substantial scientific data demonstrating that there is no significant difference between—

 - (i) The effects that the variables to be studied in the trial have on women or members of minority groups, respectively; and
 - (ii) The effects that variables have on the individuals who would serve as subjects in the trial in the event that such inclusion were not required." 492B(d)(2)
9. The vast majority of human subject studies supported by NIH represent basic or exploratory research. For example, of over 10,000 active research awards involving human subjects that were identified in 1994, only some 480 fit the NIH definition of a Phase III clinical trial.
10. See *Guidelines*, *supra* note 2, at V.B. and V.I.A. for discussion of the rationale for this definition.
11. PL 103-43, *supra* note 6, at Section 492B(c); See also *Guidelines*, *supra* note 2, at III.B. and V.C. for discussion of valid analysis and specific requirements for Phase III clinical trials.
12. To discern the potential impact of the revised policy on new clinical trials, NIH staff reviewed 52 Phase III clinical trials already in progress during the transition period between enactment of the law (June 10, 1993) and its effective date (September 30, 1994). As reported by *LaRosa et al.*, *supra* note 4, at 34, it was found that most of these trials did indeed meet the new requirements. This suggests that inclusion goals had already been accepted and incorporated into study designs by NIH grantees, and that the new requirements would not create a major obstacle to designing and conducting clinical research for this community of researchers.
13. *Nadel*, *supra* note 5, at 5.
14. As part of this effort, NIH staff conducted formal training classes for over 1,000 NIH administrative staff with review, program, or grants management responsibilities in the autumn of 1994. In addition, written materials were distributed to hundreds of non-governmental scientists who serve in an advisory capacity as reviewers on NIH Study Sections or Initial Review Groups.
15. By July 1995, ORWH completed analysis of the 18 written responses received during the one-year public comment period. The inclusion of women as subjects in clinical research was not raised as an issue in any of these responses. Most of the public comments dealt with minority groups and their subpopulations and expressed concerns about difficulties in recruiting sufficient numbers of these subjects, particularly in certain geographic regions. A number of respondents expressed serious concerns about the cost of expanding clinical trials to meet the inclusion requirements. Others disagreed with the broad definition of clinical research used in the Guidelines.
16. U.S. Department of Health and Human Services, National Institutes of Health. *Questions and Answers Concerning the 1994 NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. September 7, 1994.
17. Recommendations for awards are presented to the institute advisory councils which meet three times a year, typically January-February, May-June, and September-October. During the first council round that the new policy was in place, 7.62% of all applications involving human subjects were found to be unacceptable, with regard to gender/minority inclusion, and thus received an administrative bar-to-funding. Conversely, it may be inferred that the policy had indeed been well communicated to the scientific community, because over 92% of new applications describing human subject research were found to meet the standard as submitted. Of the 411 applications that received such administrative bars during this period, 45 were paid after NIH program staff worked with applicants to resolve the deficiencies in gender/minority inclusion that were found during initial review. For example, the applicant may address concerns by furnishing additional information about the study design or by agreeing to modify the composition of the study population.
18. The recommendations of the IOM committee are set out in Mastroianni, A.C., R. Faden, and D. Federman (eds.). 1994. *Women and Health Research. Ethical and Legal Issues of Including Women in Clinical Studies*. Institute of Medicine. National Academy Press, Washington, D.C; a succinct summary of these recommendations may be found in K.H. Rothenberg. *The Institute of Medicine's Report on Women and Health Research: Implications for IRBs and the Research Community*. IRB (forthcoming 1996).
19. *Rothenberg*, *supra* note 18, citing *Mastroianni et al.*, *supra* note 18, at 15.
20. *Id.*
21. *Id.*
22. *Id.* at 17.
23. For example a pregnant woman could be appropriately excluded from a study of hormone replacement or contraception. See *Rothenberg*, *supra* note 18, citing *Mastroianni et al.*, *supra* note 18, at 17.
24. U.S. Department of Health and Human Services, National

- Institutes of Health. Recruitment and Retention of Women in Clinical Studies. A Report of the Workshop Sponsored by the Office of Research on Women's Health. NIH Publication 95-3756.
25. U.S. Department of Health and Human Services, National Institutes of Health. Outreach Notebook for the NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. 1994.
 26. For a full discussion of liability implications see K.H. Rothenberg. Gender matters: implications for clinical research and women's health care, *HOUSTON L. REV.* (forthcoming February 1996); See also *Mastroianni et al.*, *supra* note 18, at 150.
 27. *Rothenberg*, *supra* note 26, citing *Mastroianni et al.*, *supra* note 18, at 150.
 28. As noted in *Mastroianni et al.*, *supra* note 18, at 13, "It is impossible to quantify the risk of tort liability from the inclusion of women in clinical studies at this time, because: (1) there is no complete compendium of unreported cases involving settlements and (2) pregnant women and women of childbearing age have not been included in some major studies in the past." See also *Mastroianni et al.*, *supra* note 18, at 151.
 29. *Rothenberg*, *supra* note 26, citing *Mastroianni et al.*, *supra* note 18, at 150.
 30. *Id.*
 31. See 45 C.F.R. part 46, subpart A (1994), Sections 46.116-46.117 for a full description of informed consent requirements and Institutional Review Board (IRB) responsibilities with regard to documentation and oversight. Further, according to Section 46.109(e), the IRB "shall have the authority to observe or have a third party observe the consent process and the research."
 32. As noted by *Rothenberg*, *supra* note 26, "In the context of research, a battery action may be brought if the participant is subjected to a study without her knowledge or consent. If the initial consent to participation did not include adequate disclosure of risks and alternatives, the legal action will be based on negligence for lack of informed consent."
 33. As noted by *Rothenberg*, *supra* note 26, "Federal regulations, as well as FDA guidelines, require researchers and IRBs to obtain the informed consent of all persons who participate in clinical research. The standard for what is truly 'informed' consent varies from state to state, but in general, three standards exist in the context of medical malpractice. Some states allow a physician to disclose a level of information regarding risks and benefits that is customary for physicians practicing in the community. Some states require physicians to disclose all information that a 'prudent person' in the patient's position would want to know. In a few states, a more subjective standard has been adopted, requiring physicians to disclose all information needed to allow the particular patient to make an informed decision. Recently a federal court held that a higher standard of informed consent, a duty to inform a potential participant of all 'reasonably foreseeable' risks, is required for participation in non therapeutic research injury cases." See also *Mastroianni et al.*, *supra* note 18, at 156, citing *Whitlock v. Duke University*, 637 F. Supp. 1463 (M.D.N.C. 1986), *aff'd*, 829 F.2d 1340 (4th Cir. 1987).
 34. As noted by *Rothenberg*, *supra* note 26, "The first, and fairly clear-cut, case would involve participation in a clinical trial where the treatment received was therapeutic for the fetus. In such a case, it is unlikely that liability would be found when informed consent to the treatment was provided to further the best interests of the fetus and improve its health." See also *Mastroianni et al.*, *supra* note 18, at 162, citing *Roberts v. Patel*, 620 F. Supp. 323 (N.D. Ill. 1985) (the informed consent of the mother is sufficient to insulate a drug manufacturer from liability where the treatment is designed to be therapeutic for the fetus).
 35. As noted by *Rothenberg*, *supra* note 26, citing *Mastroianni et al.*, *supra* note 18, at 162-3, "Some commentators have reasoned that the result would be less clear if participation in the clinical trial was sought because the experimental treatment or drug was designed to be therapeutic for the mother only. In such a case, liability might rest on an analysis of the seriousness of the mother's illness, the risks to the fetus, and the existence of any safer alternatives."
 36. As noted by *Rothenberg*, *supra* note 26, citing *Mastroianni et al.*, *supra* note 18, at 162, "There have been only two cases of reported research injuries to offspring. In both cases, the University of Chicago was found liable because it had failed to obtain consent to experiment with DES on pregnant women."
 37. *Rothenberg*, *supra* note 26, citing *Mastroianni et al.*, *supra* note 18, at 163-164.
 38. *Id.*, at 166.
 39. See *Rothenberg*, *supra* note 26.
 40. Pinn, V.W. 1994. The role of NIH's Office of Research on Women's Health. *Academic Medicine* 69: 698-702; See also *Mastroianni et al.*, *supra* note 18.
 41. Pinn, V.W. 1995. Equity in biomedical research. *Science* 269: 739.
 42. *LaRosa et al.*, *supra* note 4, at 36.

***Eugene G. Hayunga, Ph.D., is Research Policy Officer in the Office of Research on Women's Health, National Institutes of Health. Karen H. Rothenberg, J.D., M.P.A. is Marjorie Cook Professor of Law and Director of the Law and Health Care Program of the University of Maryland at Baltimore; she is presently on leave as Special Assistant to the Director of the Office of Research of Women's Health. Vivian W. Pinn, M.D. is Associate Director for Research on Women's Health of the National Institutes of Health, and Director of the Office of Research on Women's Health. This article was prepared specifically for the *Digest* and is based, in part, on Dr. Hayunga's presentation during the New York State Bar Association's Food, Drug and Cosmetic Law Section's program entitled "Clinical Research and Products Liability Issues: Use of Women of Childbearing Potential in Drug Trials" (New York City, October 30, 1995).**