Impact of Research Policy on Participation of Individuals of Reproductive Age

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MotherToBaby

OTIS
Organization of Teratology Information Specialists

No conflicts of interest to report.

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Timeline of Regulations

Late 1950s-1960s- Thalidomide Tragedy

1966-FDA developed the segment I, II, and III testing protocols

1975- Dept. of Health, Education and Welfare published 45 CFR 46 **Subpart B**

1977- FDA guidelines for drug development

1979- Belmont Report

1981- HHS and FDA revised their human subjects' regulations

1984- Public Health Service task force

1990- NIH Office of Research on Women's Health established

1991-Federal Policy for the Protection of Human Subjects or the "Common Rule"

1993- NIH Revitalization Act of 1993

1993- FDA "Guidelines for Study and Evaluation of Gender Differences in the Clinical Evaluations of Drugs"

1994- NIH "Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research"

1994- Institute of Medicine Committee on Ethical and Legal Issues Related to Inclusion of Women in Clinical Studies recommendation

2001- DHHS final rule revising Subpart B

2004- Draft FDA Guidance: "Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling"

2016- The 21st Century Cures Act

2018- Revised Common Rule

2018- FDA Draft Guidance: "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials"

2020- NIH "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry"

1975-
45 CFR 46 Subpart B

- Regulations pertaining to research involving pregnant women
- Based on **presumption of exclusion of pregnant women from research**
- "A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery." 45 CFR 46.202(f)

1977-
FDA Guidelines for Drug Development

- Recommended **women of childbearing potential be excluded from Phase I and early Phase II trials of new drugs**
- IRBs and PIs tended to extend this policy to **all phases** of drug development
- Limited discussion about the risks and potential benefits

1979-
The Belmont Report

1. Respect of Persons
2. Beneficence
3. Justice

1984-

Public Health Service task force

- Long-standing lack of research in women's health had compromised the quality of available information on diseases affecting women
- This lack can be attributed to regulations barring participation of women of childbearing potential (1977 FDA regulation)

1990-

NIH Office of Research on Women's Health (ORWH)

- Concerns about the systematic and consistent lack of women included in NIH-supported research.
- "A 1990 General Accounting Office study of NIH grant applications—most relating to conditions affecting both men and women—found that **about 20% of them provided no information about the sex of the study population**." (ORWH)

1991-

Federal Policy for the Protection of Human Subjects or the "Common Rule"

- Codified in separate regulations by 15 Federal departments and agencies
  - DHHS: 45 CFR 46
  - FDA: 21 CFR part 56, Institutional Review Boards, and 21 CFR part 50, subpart B, Informed Consent of Human Subjects

1993-

NIH Revitalization Act of 1993

- Directed the NIH **to establish guidelines for inclusion of women and minorities in clinical research**
- Requires NIH to ensure that clinical trials are carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied affect women or members of minority groups differently than other trial participants. https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm
- BUT **did not require that results be disaggregated by sex, which limits generalizability of research findings**

1993-

FDA "Guidelines for Study and Evaluation of Gender Differences in the Clinical Evaluations of Drugs"

- Articulated the agency's decision to reverse the 1977 policy that barred most women from participating in the early phases of clinical trials

1994-

NIH "Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research"

- States, "women…must be included in all NIH-supported biomedical and behavioral research projects involving human subjects unless a clear and compelling rationale and justification establishes…that inclusion is inappropriate."

1994-

Institute of Medicine (IOM)

- Committee on Ethical and Legal Issues Related to Inclusion of Women in Clinical Studies
- Recommended that women should be enrolled as participants in clinical studies (Gordon et al., 2006)

2001-

DHHS final rule revising Subpart B

- Revised rule creates a policy of **presumed opportunity for pregnant women to participate in research**

2016- The 21st Century Cures Act

- Clinical trials must provide results of valid analyses by sex/gender, race, and ethnicity
- "**SABV** will be factored into **research designs, analyses, and reporting** in vertebrate animal and human studies."
- Strong justification…must be provided for applications proposing to study only one sex."
- Established Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

2018- Revised Common Rule

- Subpart B remains intact
- 46.202(f) Definition of pregnancy remains intact
- No longer includes pregnant women as an example population that are potentially vulnerable to coercion or undue influence

2018- FDA Draft Guidance: "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials"

- "Apply both to clinical trials that enroll pregnant subjects and to clinical trials that allow enrolled subjects who become pregnant to remain in the trial."
- And, "Filling the knowledge gaps regarding safe and effective use of drugs in pregnant women is a critical public health need, but one that raises complex issues."

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted **and provide data for assessing potential risks to pregnant women and fetuses**;

(b) **The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman** or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) **Any risk is the least possible** for achieving the objectives of the research;

(d) If the **research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus** when risk to the fetus is not greater than minimal **and** the purpose of the research is the **development of important biomedical knowledge that cannot be obtained by any other means**, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

45 CFR 46 SUBPART B

(e) If the research holds out the prospect of **direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in** accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is **fully informed** regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) **For children** as defined in §46.402(a) who are pregnant**, assent and permission are obtained** in accord with the provisions of subpart D of this part;

(h) **No inducements, monetary or otherwise, will be offered to terminate a pregnancy**;

(i) Individuals engaged in the research **will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;** and

(j) Individuals engaged in the research **will have no part in determining the viability of a neonate**.

45 CFR 46 SUBPART B

- FDA does not have regulations like Subpart B and recommends that Subpart B (along with other DHHS regs) be followed in the conduct of FDA-regulated research. Do offer provide guidance documents:
  - "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials" draft guidance
  - "Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling" Draft Guidance

Phase I- First in Human

- Usually only healthy populations, but FDA allows researchers to jump to affected patient population with some diseases, esp. if deadly (HIV, hep, cancer).
- FDA/sponsors often reluctant to include women of childbearing potential (WOCP) in this Phase, since teratogenicity unknown; possible with adequate contraceptive requirements

Phase II- Proof of Concept

- "For drug development programs where there are plans to enroll pregnant women in a phase 3 clinical trial, PK data in pregnant women should be collected during the phase 2 clinical trials to guide appropriate dosing in phase 3." FDA Pregnant Women guidance

Phase III- Safety and Efficacy

- Phase I and Phase II clinical trials in a nonpregnant population that include females of reproductive potential should be completed before sponsors enroll pregnant women in later phase clinical trials." FDA Pregnant Women guidance

Phase IV Post-marketing studies

- Conducted after a treatment is approved for use by the FDA, provide additional information including the treatment or drug's risks, benefits, and best use.
- When most PK studies in pregnant women will occur, using pregnant women who have already been prescribed the drug as a therapy by their physician. – FDA PK in Pregnancy guidance

Other Considerations

- Safety as endpoint exists in all phases
- "When pregnant women are enrolled in a clinical trial, data collection elements should include, at a minimum: gestational age at enrollment; gestational timing and duration of drug exposure; and pregnancy outcomes including adverse maternal, fetal, and neonatal events…Infants born to mothers who were exposed to the investigational drug should have follow-up safety information collected." FDA Pregnant Women guidance

Autonomy Considerations

- "All women are pregnable and therefore always pregnant."- (Merton, 1993)
- Overly paternalistic? Shouldn't women be the ones who make the decision about the risk of their participation?
- If you do become pregnant:
  - Unblinding should occur so counseling may be offered based on whether the fetus has been exposed to the investigational drug, placebo, or control. (FDA Pregnant Women Guidance)
  - The risks and benefits of continuing versus stopping investigational treatment can be reviewed with the pregnant woman. (FDA Pregnant Women Guidance)

RESPECT FOR PERSONS

Informed Consent

- IOM recommends including these items in the initial consent form (Gordon et al., 2006):
  1. Risks to reproduction and potential offspring
  2. Birth control considerations and risk of failure
  3. Voluntarily select contraceptive method of choice and pregnancy termination options
  4. Notifying the investigator of a suspected pregnancy
- If pregnancy occurs during a clinical trial, pregnant women who choose to continue in the clinical trial should undergo a second informed consent process that reflects these additional risk-benefit considerations. (FDA Pregnant Women guidance)

RESPECT FOR PERSONS

Contraceptive Options

- If requiring contraception or abstinence as a condition to participate, needs to have strong scientific justification
- Consideration of failure rates and what is "adequate contraception"
- Requiring Abstinence is only reasonable for short term studies, still ethically questionable
- Confidentiality concerns when asking about sexual activity, especially if it involves minors

RESPECT FOR PERSONS

Do not harm:

- **Moral duty to avoid harm to the fetus** is the most common rationale for excluding women from research. The risk of fetal harm leads to this exclusion.

Risk-benefits assessment:

- "Risks are not research-related when they are independent of the study and not associated with a trial intervention or protocol requirements. In other words, **when a study collects data about drug treatment during pregnancy but the drug was prescribed before study enrollment by the patient's HCP, then the risks associated with the drug use are not research-related risks** (Sheffield et al. 2014)." FDA Pregnant Women guidance
- "There may be circumstances in which a clinical trial can potentially expose a fetus to greater than minimal risk. Pregnant women can be enrolled in clinical trials that involve greater than minimal risk to the fetuses **if the trials offer the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses**." FDA Pregnant Women guidance
- "When an IRB considers whether to approve a protocol involving pregnant women, it should **consider only those risks and benefits** (direct to the subjects, or generalizable knowledge) **that may result from the research itself** (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research) (21 CFR 56.111(a)(2))." FDA Pregnant Women guidance

BENEFICENCE

Distribution of Research Burdens and Benefits

- "The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring).- 21 CFR 312.2
- Some argue if results are sex-integrated then difficult to obtain "clean" data. (Gordon et al., 2006)
- This same argument can be applied to pregnant vs. non-pregnant. How can results from non-pregnant be extrapolated to pregnant populations?

Some have argued it's unethical and illegal to exclude pregnant women from clinical research.

- "Given the large number of pregnant women who need prescription medicines to maintain their health, some have argued that it is unethical not to obtain dosing information in this subpopulation (Faden 2000). Others recommend that only pregnant women who need a drug for therapeutic reasons be included in clinical studies, citing that drug studies cannot be done in "normal pregnant volunteers" (Stika 2001). (FDA PK Guidance)

JUSTICE

ADDITIONAL IRB CONSIDERATIONS

- Regulations are the floor: IRBs should determine if any additional safeguards are needed in the clinical trial to protect the rights and welfare of pregnant participants
  - Guidance documents intended to help with those determinations, provide framework for internal policy and procedure decisions.
- What if the pregnant (or potentially pregnant) participants are minors? Local/state law would need to be considered and 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigation would also apply.
- Privacy/confidentiality concerns about collecting information about participants sexual status and history
- Others from your IRB?

REFERENCES

Books and Articles

Gordon et. al. (2006). Chapter 9-4: Requiring Birth Control to Participate in Research, In E.A. Bakert and R.J. Amdur (Eds.), *Institutional Review Board: Management and Function, 2nd Edition* (pp. 351-355). Jones and Bartlett Publishers, 2006.

James H. Kim, Anthony R. Scialli, Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease, *Toxicological Sciences*, Volume 122, Issue 1, July 2011, Pages 1–6, https://doi.org/10.1093/toxsci/kfr088

Merton, Vanessa, The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. Women) from Biomedical Research (1993). *American Journal of Law and Medicine*, Vol. 19, 1993, Available at SSRN: https://ssrn.com/abstract=1292951

Way, Cynthia. (2006) Chapter 9-3: Phase I Clinical Trials in Healthy Adults. In E.A. Bakert and R.J. Amdur (Eds.), *Institutional Review Board: Management and Function, 2nd Edition* (pp. 346-350). Jones and Bartlett Publishers.

Websites

Buchanan, Lisa. (2017, November 6). *Brief Overview of the Revised Common Rule and Subpart B –Pregnant Women*. Office for Human Research Protections. Retrieved May 30, 2023, from https://www.nichd.nih.gov/sites/default/files/2017-11/4-OverviewNew_Rule_SubpartB.pdf

Food and Drug Administration (2018, January 4). *Step 3: Clinical Research*. Retrieved May 30, 2023, from https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#phases

Food and Drug Administration (2018, January 4). What Are the Different Types of Clinical Research?. Retrieved May 30, 2023, from https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research

National Institutes of Health- Office of Research on Women's Health (n.d.). *About*. Retrieved May 30, 2023, from https://orwh.od.nih.gov/about

National Institutes of Health- Office of Research on Women's Health (n.d.). *Office of Research on Women's Health Historical Timeline—30 Years of Advancing Women's Health*. Retrieved May 30, 2023, from https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH21_Timeline_508C.pdf

National Institutes of Health- Grants & Funding (n.d.). *Inclusion of Women and Minorities as Participants in Research Involving Human Subjects*. Retrieved May 30, 2023, from https://grants.nih.gov/policy/inclusion/women-and-minorities.htm

National Institutes of Health- Grants & Funding (n.d.). *NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research*. Retrieved May 30, 2023, from https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm

REFERENCES

Legislation, Policy, and Guidance Documents

Department of Health, Education, and Welfare- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

Department of Health and Human Services- Food and Drug Administration. (2020) *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry.* https://www.fda.gov/media/127712/download

Department of Health and Human Services- Food and Drug Administration. (2018). *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry* (Draft Guidance). https://www.fda.gov/media/112195/download

Department of Health and Human Services- Food and Drug Administration. (2004). *Guidance for Industry Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling* (Draft Guidance). https://www.fda.gov/media/71353/download

National Institutes of Health. (1994). *NIH guidelines for the inclusion of women and minorities as subjects in clinical research.* http://grants.nih.gov/grants/guide/notice-files/not94-100.html

The 21st Century Cures Act - H.R.34 - 114th Congress (2015-2016): 21st Century Cures Act. (2016, December 13). https://www.congress.gov/bill/114th-congress/house-bill/34/text

Protection of Human Subjects, 45 C.F.R. 46 (2018). https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46

Protection of Human Subjects, 45 C.F.R. 46 Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (2018). https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46#subpart-B

Investigational New Drug Application, 21 C.F.R. 312 (1987). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312

21 CFR part 56, Institutional Review Boards, and 21 CFR part 50, subpart B, Informed Consent of Human Subjects