International perspectives and guidance on Pregnant Women as Participants in Clinical Trials

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Layout

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  - Declaration of Helsinki
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Why the exclusion of women from clinical trials?

- The world has been influenced by the publicity surrounding two unfortunate events that were publicized widely.
- **NOTE:** None of these events were research.
- In each case, the problem was that research had not been done to validate the use of the product.
- Events stand as powerful metaphors for the challenges involved in research involving women who are or who might become pregnant.
- **Thalidomide** (1950s)and **Dalkon Shield** (1970s) Tragedies.

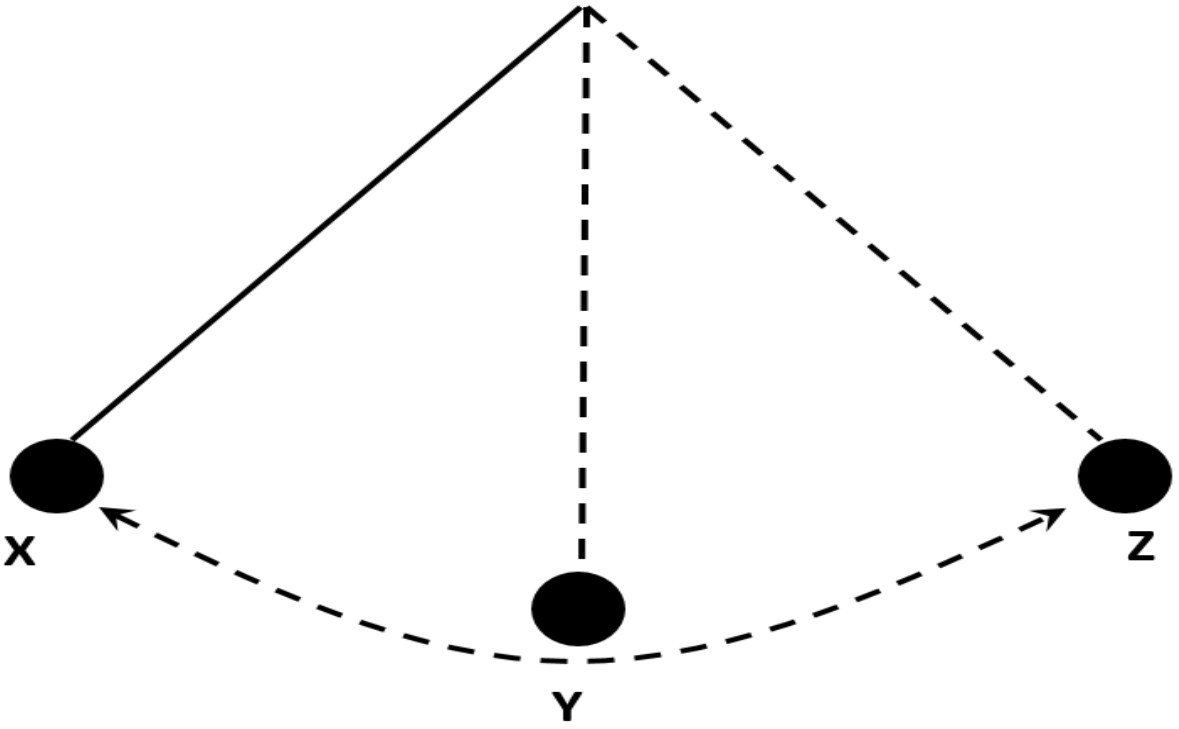
Tightening Screws on inclusion of women: US REGs

- In 1977, the FDA issued a guideline for the clinical evaluation of drugs that called for the exclusion of "women with childbearing potential," from the early phases of most clinical studies (U.S. Department of Health, Education and Welfare [US HEW]: Food & Drug Administration [FDA], 1977).
- **NOTE:** FDA guideline had excluded women of childbearing potential only from Phase I and II of clinical trials (drug safety is the primary focus).
- Sponsors often interpreted the restriction more broadly and limited entry of women into the later phases of drug trials.

The after-effects

- The two tragedies have led to tightening of Regulations on drug approvals.
- They have scared researchers, drug manufacturers and IRBS/ RECs.
- There is now the culture of avoidance/exclusion of pregnant women from clinical trials.
- Research funders are scared of litigations – IRBs/RECs are scarred of blame – Researchers are hesitant to argue for inclusion of pregnant women.
- Pregnant women often labeled as vulnerable – due to fears around the negative impact of study drugs to the fetus.
- YET pregnant women are not immune to diseases.

The Human Research Protection **Pendulum**



Minimal/Zero Protection

Reasonable protection

Overprotection

Exclusions: What has this meant for pregnant women?

- Do not enroll women who are pregnant (exclusion criteria)
- Do not enroll women intending to fall pregnant during study period.
- Periodic/monthly testing for pregnancy
- Women are made to agree not to become pregnant during study duration.
- Withdraw of women who become pregnant while participating
- Preventing pregnancy among all enrolled women up to end of participation 5 year trials by using dual pregnancy prevention methods
- Withdrawal of test product
- Termination of study participation
- For some studies, pregnant adolescents (below 18) are excluded.

US REGULATIONS – 1991

- The Common Rule includes additional **protections for certain vulnerable research subjects**:
  - **Subpart B** provides additional protections for pregnant women, in vitro fertilization, and fetuses
  - Subpart C contains additional protections for prisoners
  - Subpart D does the same for children.
- In 2001, the wording of the U.S. regulations was changed to indicate that pregnant women may be involved in research if ten stated conditions are met.
- In 2001, the FDA also issued guidance on pharmacokinetic studies during pregnancy, clinical lactation studies, and pregnancy exposure registries (Blehar, et al. 2013).

OBSERVATIONS Re US REGs:

- Studies proposing the involvement of vulnerable populations are reviewed to ensure that inclusion of these participants is justified and, if so, that adequate procedures are in place to minimize the risks related to physical harm, psychological harm and breach of privacy and confidentiality.
- The research must be relevant to the vulnerable population and not otherwise capable of being carried out with a non-vulnerable population.

ICH GCP 1996

- Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
- (a) That the trial involves research.
- .....
- (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, **to an embryo, fetus, or nursing infant.**

CIOMS

- Guidelines 18 and 19 concern women participating in research.
- Women should not automatically be excluded from research because of the possibility that they could become pregnant.
- **CIOMS allows for research with pregnant women and provides some conditions.**
- Rather, the researchers should inform potential subjects of the study-related risks in becoming pregnant and offer pregnancy testing and "access to effective contraceptive methods before the research commences."
- If a woman is pregnant, she may be included in research provided she is informed of risks, the research is relevant to the pregnancy, and animal models have previously examined teratogenic risk.
- CIOMS emphasizing on justice (fair access/inclusion)

CIOMS …some details

- Addresses women who become pregnant during research.
- **Serious harm and access to abortion:** Research with pregnant women must be conducted only in settings where these women can be guaranteed access to a safe, legal abortion.
- Requires plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child (Guideline 19);
- ICF – detailed information on risks etc required.

Declaration of Helsinki – 2013 version

- 13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
- DOH is silent on inclusion of pregnant women in CTs.
- The statements on Vulnerable Groups and Individuals does not include women.

UNAIDS Ethical Considerations in Biomedical HIV Prevention Trials (2012)

- **UNAIDS allows for research with pregnant women and provides some conditions.**
- Guidance Point 9 encourages the inclusion of women in HIV clinical trials including those who are "sexually active and may become pregnant, be pregnant or be breastfeeding" because they should be future recipient of safe and effective HIV prevention interventions.

European Documents

- Council of Europe: *Council of Europe Treaty Series - No. 195:* Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research :Strasbourg, 25.I.**2005**
- REGULATION (EU) No 536/**2014** OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- Council of Europe and EU documents allows for research with pregnant women and provide some conditions.

Global efforts to correct the pendulum

- Post 2000 we see efforts by various players to correct pendulum including DHS/FDA/NIH and EU.
- GFBR Theme for GFBR 2016 in Buenos Aires attended by more than 100 participants from various countries: Ethics of Research in Pregnancy.
- GFBR focuses on topical issues and is funded by NIH, Welcome Trust, WHO, BMGF etc
- Multi Country project aimed at studying and promoting inclusion of pregnant women in CTs.
- Post GFBR meeting in Bangkok November 2017 attended by over 30 bioethicists and experts from various countries

CONCLUDING REMARKS

- Historically, enrollment of pregnant women in clinical research studies encountered many barriers based on risk aversion, lack of knowledge, and regulatory ambiguity.
- Access/fair inclusion: Pregnant women are often "over-excluded" from clinical and preventive intervention trials We are witnessing a corrective movement of the pendulum.
- There is lack of Research Evidence for Medications to Treat Pregnant Women
- Pregnant women are not a vulnerable group but a special group.
- International guidelines allow for research with pregnant women.
- We are moving away from -inclusion of these participants should be justified to exclusion should be justified.
- Researchers, RECS, Sponsors, Society have roles to play in correcting the pendulum.
- After all... pregnant women become ill and sick women become pregnant.