ชมรมจริยธรรมการวิจัยในคนในประเทศไทย
Forum for Ethical Review Committees in Thailand

Research Involving Pregnant Women, Fetuses, and Neonates

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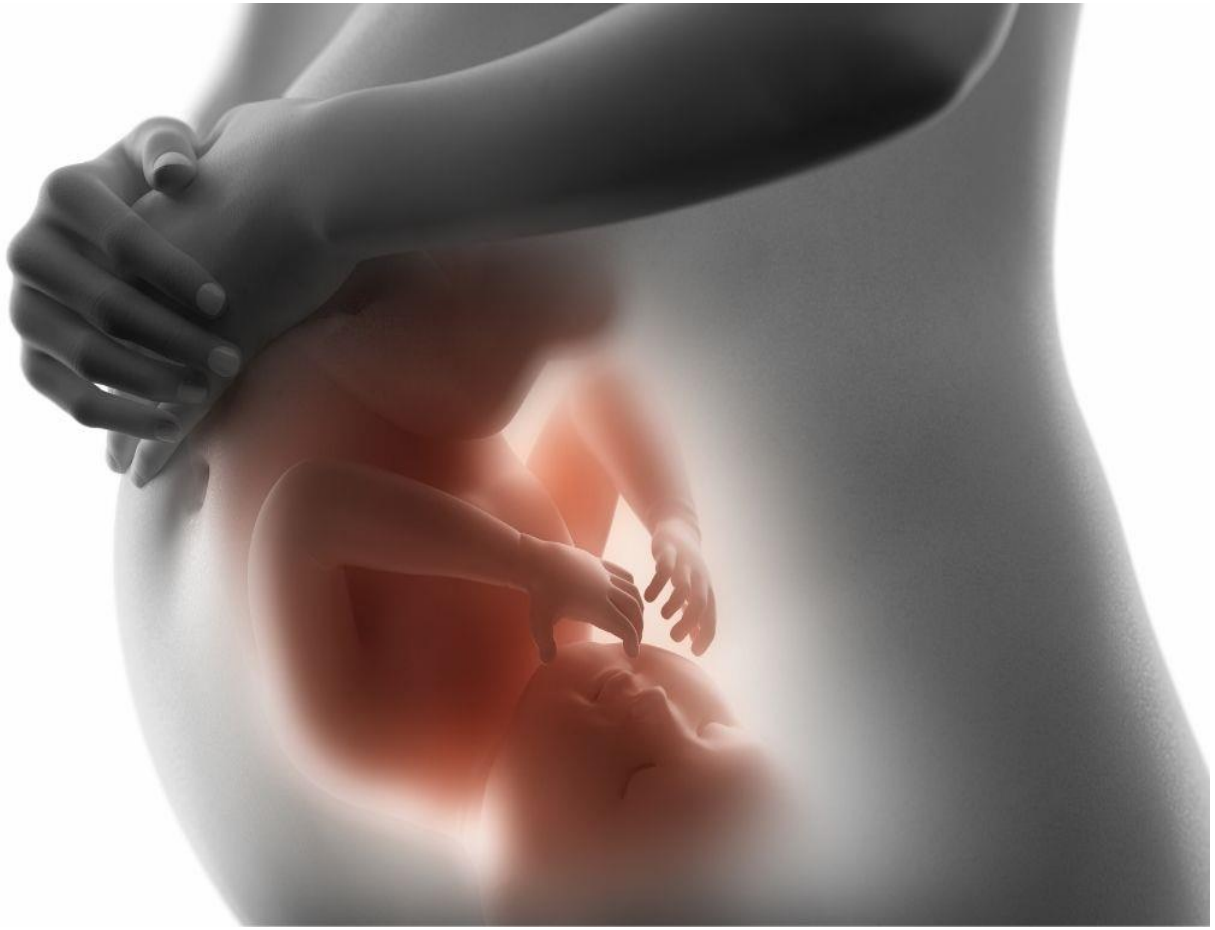
วิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า

Outline

- History of women as subjects of research
- Regulations
- Type of research permitted
- Informed consent

Research Involving Pregnant Women, Fetuses, and Neonates



Types of Vulnerability

1. **Capacity to consent**
   - *Children and adolescents*
   - *Adults incapable of giving informed consent*
2. **Individuals in hierarchical relationships**
   - *Medical and nursing student*
   - *Members of the armed forces*
   - *Hospital personnel*

CIOM 2016

Types of Vulnerability

3. **Institutionalized persons**
   - *Residents of nursing homes, mental institutions, prisons*
4. **Women**
   - *Trafficked women*
   - *Asylum seekers*
   - *Women in a cultural context not permitted to consent on their own behalf.*

CIOM 2016

Types of Vulnerability

5. **Pregnant women**
   - *Mother and fetus*
6. **Other potentially vulnerable individuals**
   - *Poor, unemployed people*
   - *Racial minorities*
   - *Refugees, homeless persons*
   - *People with incurable diseases*

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Pregnant women and fetuses as subjects: History

1930s

- Used ex-utro fetal tissue as an object of experimentation
- Production and testing of vaccines
- Propagation of human viruses
- Testing of biological products

1954

- Utilized human fetal kidney tissue cell lines to grow poliovirus in culture

- 1940
  - Discovery of birth defects resulting from fetal exposure
- 1970
  - New awareness of the teratogenic potential of prescription drugs
  - Diethystilbestrol (DES)
  - Thalidomide

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PLLR: Pregnancy and Lactation Labelling Rule

Regulations for Protection of Human Subjects 45 CFR 46

- **Subpart A** – basic HHS Policy - "The Common Rule" is the common name for this policy that many other federal departments & agencies have adopted
- **Subpart B** - Pregnant Women, Human Fetuses, and Neonates
- **Subpart C** - Prisoners
- **Subpart D** - Children

45 CFR 46: Subpart B

- Allows research involving pregnant women or fetuses only if
  - Appropriate studies on animals and non-pregnant individuals have been completed
  - Research is not intended to meet the health needs of the mother or the fetus
  - *The risk to the fetus must be minimal*

45 CFR 46: Subpart B

- No specific guidance regarding the definition of “minimal risk”
- The risk to the fetus must be minimized to the greatest extent possible

	Benefit to mother or Fetus	No benefit
Minimal Risk	Allowed	Allowed if purpose is development of important biomedical knowledge
Greater Than Minimal Risk	Allowed if risk to fetus is the least possible	**Not allowed**

45 CFR 46: Subpart B

- Excludes researchers from any decisions as to the timing, methods, or procedures used to
  - Terminate a pregnancy
  - Determinations on the viability of the fetus at the termination of the pregnancy
- Should be conducted only if consent is obtained from the mother, or from both parents

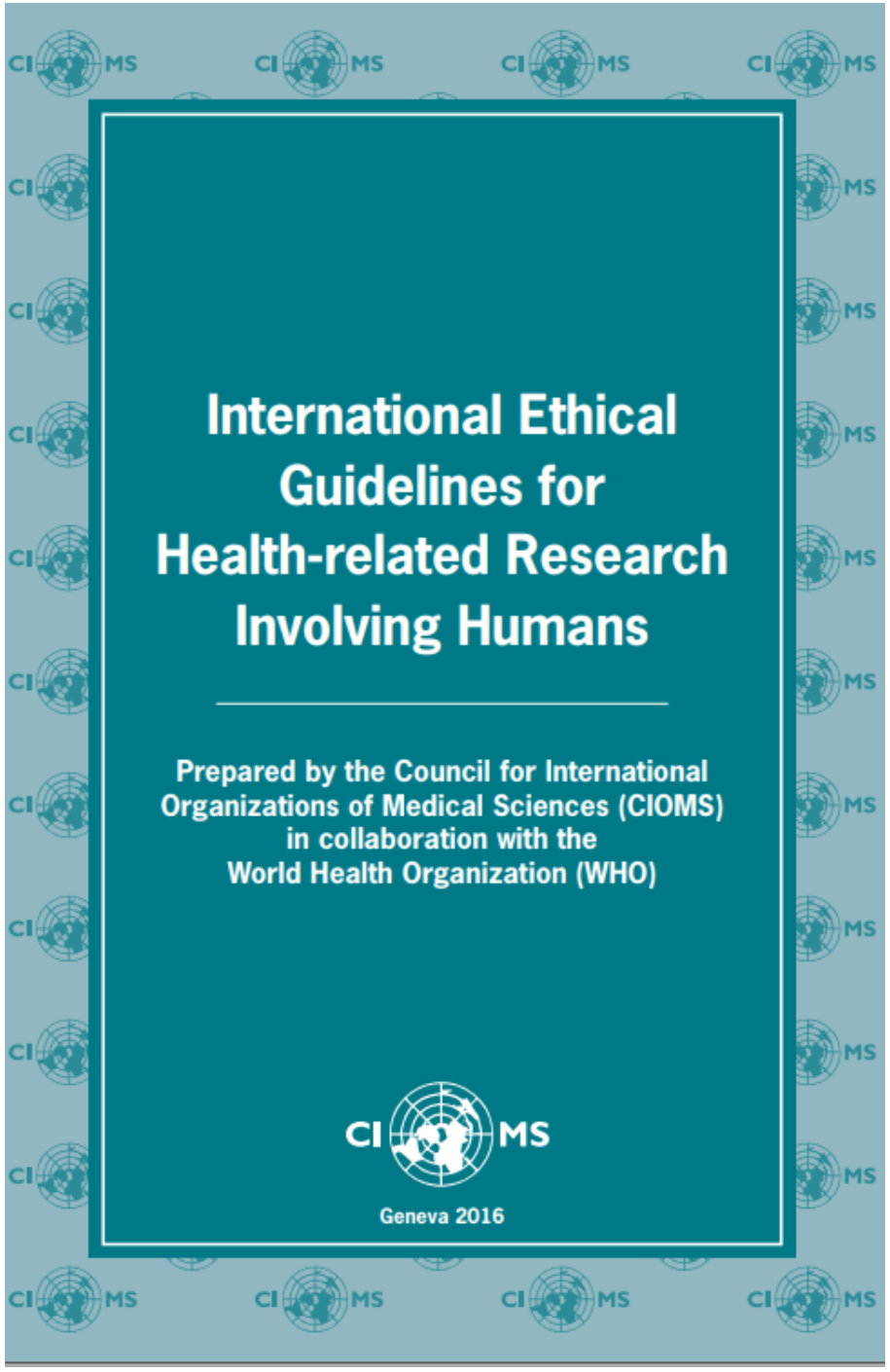
Pharmacokinetic process	Physiological changes during pregnancy	Pharmacokinetic modification
Absorption	Decrease gastric acidity	Altered absorption
	Decrease emptying	Delayed absorption
	Decrease gastrointestinal motility	Decreased maximum concentration
	Increase blood flow in skin, mucose membrane and muscles	Increased intramuscular bioavailability and external administration
Distribution	Increase total body water	Increased volume of distribution of hydrophilic and lipophilic drugs
	Decrease protein concentration	Increased free fraction of drugs
Metabolism	Increase or decrease enzymatic activity	Altered hepatic clearance
	Cholestasis	Decreased biliary elimination
Renal excretion	Increase renal blood flow and GFR Decrease tubular reabsorption	Increased renal clearance

Pharmacokinetic process	Physiological changes during pregnancy	Pharmacokinetic modification
Absorption		
Distribution		
Metabolism		
Renal excretion		

Risk and Benefit Assessment

- Investigator qualifications/ facilities
- COI management
- Source of funding
- Protocol design
- Inclusion/Exclusion
- Adequate sample size
- Distribution and method of randomization

CONSENT IS REQUIRED FROM:	WHEN THE RESEARCH HOLDS OUT:
Pregnant Woman	Prospect of direct benefit to the pregnant woman Prospect of a direct benefit both to the pregnant woman and the fetus No prospect of benefit for the woman nor the fetus when risk to the fetus is NOT greater than Minimal Risk and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means
Consent of the Pregnant Woman and the Father	Prospect of direct benefit society to the fetus


International Ethical Guidelines for Health-related Research Involving Humans
Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)
CIOMS
Geneva 2016

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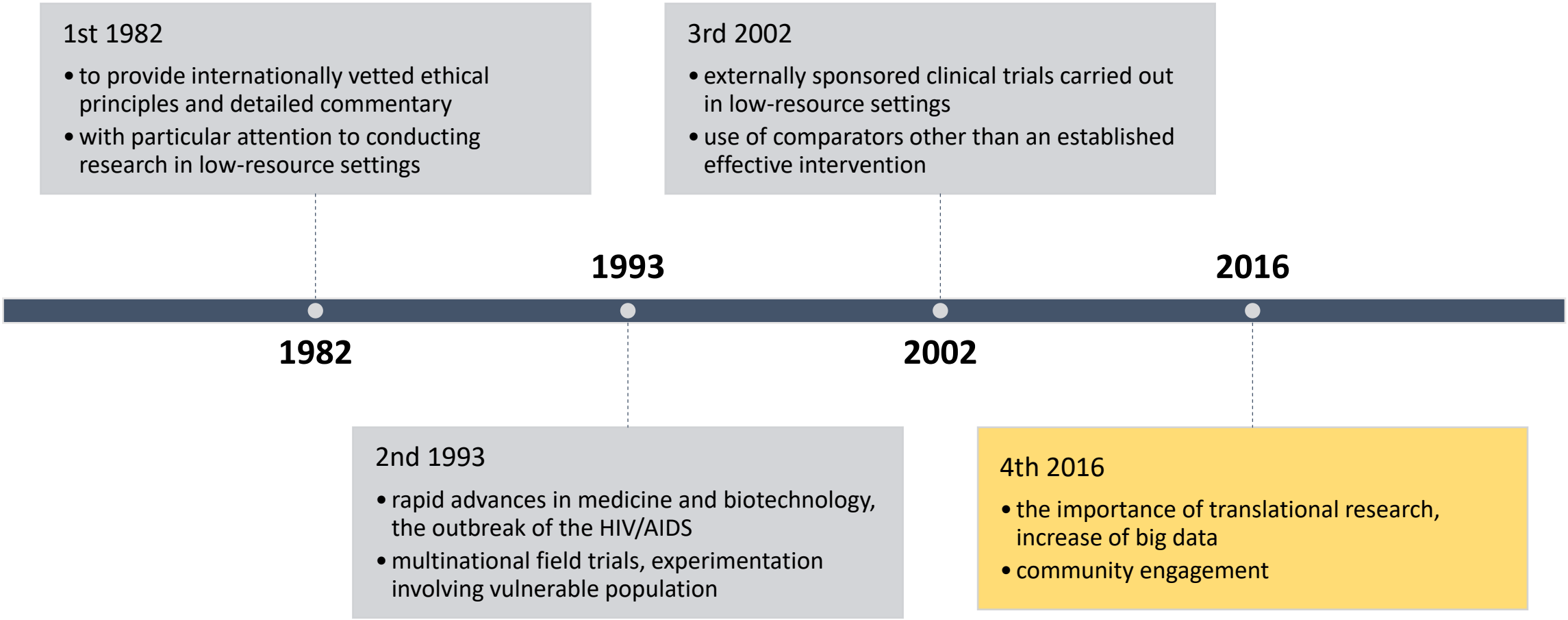


GUIDELINE 19:

PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

Pregnant and breastfeeding women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted. Research in pregnant women must be initiated only after careful consideration of the best available relevant data.

In no case must the permission of another person replace the requirement of individual informed consent by the pregnant or breastfeeding woman.

For research interventions or procedures that have the potential to benefit either pregnant or breastfeeding women or their fetus or infant, risks must be minimized and outweighed by the prospect of potential individual benefit.

For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:

- **the risks must be minimized and no more than minimal; and**

Guideline 19: PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

- Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted
- Research in pregnant women must be initiated only after careful consideration of the best available relevant data
- For research interventions or procedures that have the potential to benefit either pregnant or breastfeeding women or their fetus or infant, **risks must be minimized and outweighed by the prospect of potential individual benefit**

Guideline 19: PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

- For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:

  the risks must be minimized and no more than minimal; and
  the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or breastfeeding women or their fetuses or infants

Guideline 19: PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

When the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the *research cannot be conducted in non-pregnant or non-breastfeeding women*,

a research ethics committee may permit a minor increase above minimal risk

Guideline 19: PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

Short-term and long-term follow-up of the fetus and the child may be required in research involving pregnant and breastfeeding women depending upon the study intervention and its potential risks

Health-related research involving pregnant women that has the potential for harm to the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted

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.

Before pregnant women are enrolled, researchers must, at a minimum, determine whether fetal impairment and mental health conditions are recognized as legal grounds for abortion in that jurisdiction

If they are not, pregnant women must not be recruited for research in which there is a realistic basis for concern that significant fetal abnormality may occur as a consequence of participation in research.

Breastfeeding women

- The father may need to be consulted in research involving breastfeeding women
- If a breastfed infant may be exposed to an investigational product through the ingestion of breast milk (or it is unknown whether an infant would be exposed), such research should be conducted in accordance with Guideline 17 – Research involving children and adolescents.

Inclusion of **Pregnant Women** in Trials

- The importance of the informed consent process cannot be overemphasized.
- Attempts to minimize the risk to the pregnant woman and her fetus should be undertaken
- Rigorous monitoring should be part of the study design

Fetal Drug Research

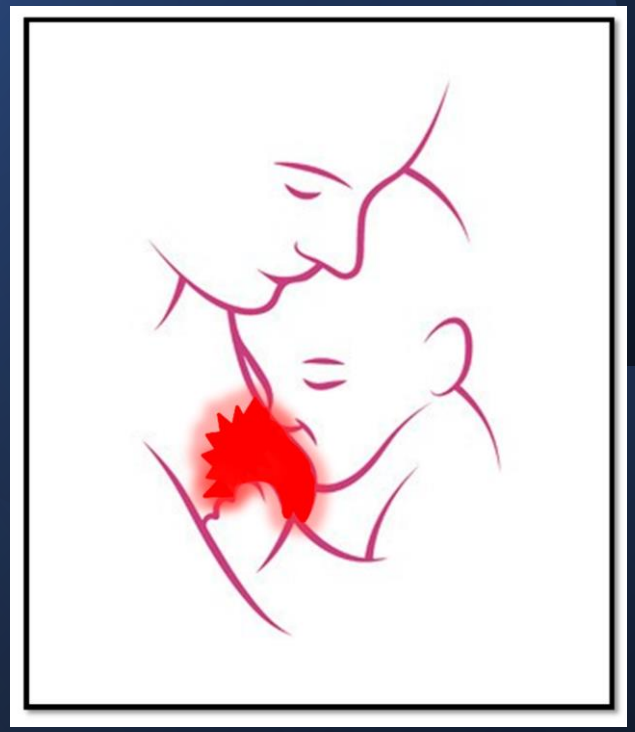
- Risks to the fetus of the proposed research may be justified by the potential benefits to the fetus
- the fetal intervention may also have implications for the pregnant woman's health, and therefore her informed consent is required and risks to the pregnant women should be minimized
- Federal regulations in the US **request involvement of the father in the consent process for research with prospect of direct benefit** solely to the fetus although this two-parent consent is controversial

Lactation Research

- A debatable ethical issue is whether one- or two-parent consent should be required, as there is potentially benefit to both the mother and the infant

- The Health Canada (Drugs and Health Products) guidance document does outline considerations for the inclusion of breastfeeding women in clinical trials, including
  - the consequences of uninformed dosages for use while breastfeeding are potentially serious and/or severe and the risk to the infant or mother is not greater than that from established procedures routinely used during breastfeeding

Lactation Research



- Many drugs taken while breastfeeding are secreted into breast milk
- The ability of a drug to be secreted into breastmilk is depended on its physicochemical characteristics,
  - Molecular size
  - Lipid solubility
  - Plasma protein-binding affinity
  - Degree of ionization
  - Does not necessarily correlate with toxicity

Research Involving Neonates

Research Involving Neonates

- Neonates
  - Uncertain viability or non-viable neonate
  - 45 CFR 46, Subpart B
- Viability
  - The ability of the fetus to survive, given the benefit of available medical therapy, to the point of independently maintaining a heartbeat or respiration
- Neonates of uncertain viability may be involved in research only if there is no added risk to the neonate, or the research ‘s purpose is to enhance the possibility of survival of the particular fetus to the point of viability

Research Involving Neonates

- If a neonate is determined to be non-viable after delivery, it may only be involved in research if
  - The neonate's vital functions will not be artificially maintained
  - The research will not terminate the heartbeat or respiration of the neonate
  - There will be no added risk to the neonate resulting from the research
  - The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.
  - Consent of a legally competent parent, or parent's LAR, is needed.

Permissible research based on levels of risk

1

Research not involving greater than minimal risk

2

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

3

Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

4

Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children

Research not involving greater than minimal risk

- Permits consideration of those experiences encountered by normal, healthy, average children in routine physical and psychological examination
  - Simple blood draw
  - Non-invasive urine collection
  - Collection of samples obtained for clinical reasons such as a tracheal fluid from routine suction of an endotracheal tube
  - Ultrasound or magnetic resonance imaging without sedation

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

- Most clinical trials in NICUs fall under this category
- IRBs should ascertain that the benefit to be accrued as derived from the research treatment itself and not the collateral benefits often associated with participation in the research
- Provision of standard clinical care otherwise not available to subjects or monetary compensation as a benefit that warrants exposing the subjects to considerable risks

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

- If a risky procedure has no potential to benefit the participant and is solely performed to collect data for research purposes, the IRB may not approve that portion of the research within the category of “prospect of direct benefit”
  - Bone marrow aspiration
  - Spinal tap
  - Imaging with sedation

Additional Consideration

- Randomization at the level of the patient will require informed consent, even when two FDA-approved medicines or two kinds of health care delivery interventions are being compared
- Consent should be sought, not because one arm of the study may be any riskier than the other, but
  - Patients and their surrogates may differ in their preferences and beliefs
  - Respect for their personhood requires that we allow them to make a fully informed decision about participation in research

Conclusion

- Well-designed and well-executed research involving neonates is essential to improve the health of infants
- Investigators, sponsors, IRBs, research institutions, regulators, and government policy-makers all play critical roles in facilitating excellence in research and ensuring participants are appropriately protected

Conclusion

- Parents are prepared to enter their neonates into clinical trials if investigators are prepared to provide clear and concise informed consent documents that clarify
  - incremental risks
  - potential benefits
- contrast these to the risks of the underlying disease and its standard treatment

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