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SCHOOL OF PUBLIC HEALTH

Human Subjects Research with Vulnerable Populations

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IHRP Human Subjects Training

April 10, 2012

Acknowledgements

- Lyn Hardy, PhD, Texas Children's Hospital
- Edward Goldman, University of Michigan
- Shaun Bhatia, UIC SPH
- UIC IRB #1

Goals

Persons attending this session will have an understanding of the:

- Definition(s) of vulnerability, ethics
- History/background for protection of vulnerable populations and ethical issues raised
- Various types of vulnerability and vulnerable populations
- Research on human subjects research with vulnerable populations
- UIC human subjects procedures for research with vulnerable populations

Part 1
Ethical Issues in Research with Vulnerable Populations

"May I never see in the patient anything but a fellow creature in pain."

Maimonides (12th Century)

"Science without conscience is the ruin of the soul."

François Rabelais, *Pantagruel* (1532)

"Never perform an experiment which might be harmful to the patient even though highly advantageous to science or the health of others.

Claude Bernard (1865)

Definitions

Basic Principles:

- Respect for persons
- Beneficence
- Justice

Definitions

- *Ethics* – the science of morality.
- *Vulnerability* – susceptible to harm
  - "those who are relatively (or absolutely) incapable of protecting their own interests."
  - Exposed to something injurious or undesirable; "Avenue of attack"
- *Harm* – social, economic, legal, psychological, and physical

Background

Increased scrutiny for vulnerable individuals is based on the basic premises of the Belmont Report – *respect for persons* and *justice*

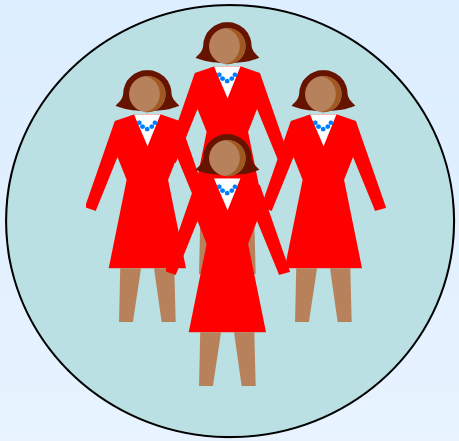
- Respect for persons: two basic ethical convictions:
  - individuals should be treated as autonomous agents,
  - "persons with diminished autonomy and thus in need of protection are entitled to such protections." National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Justice:
  - distribution of scarce benefits fits with distribution of burden – fair sharing of burdens (risks) and benefits

Who is vulnerable?

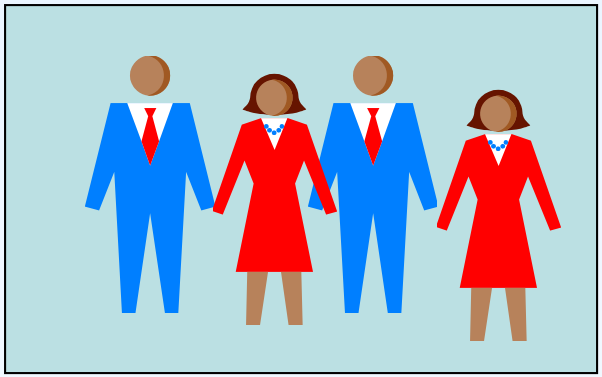
- Pregnant women
- Human fetuses
- Neonates
- Prisoners
- Children
- Persons who are:
  - physically handicapped
  - mentally disabled
  - economically disadvantaged
  - educationally disadvantaged
- Racial minorities
- Very sick
- Institutionalized

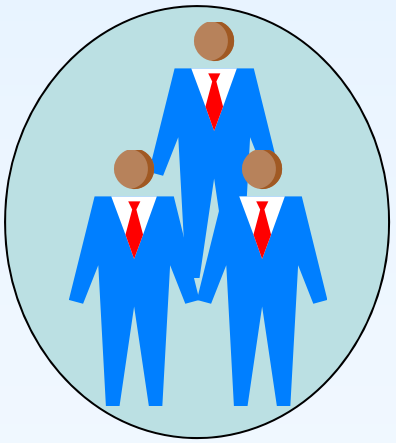
Determining Vulnerability

- Group Membership



- Determine each individual's type of vulnerability



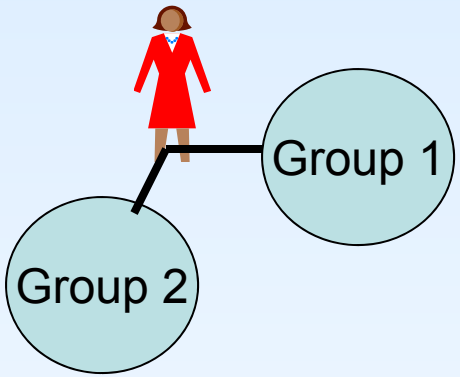


Group ID - Advantages

- Easier to identify group's vulnerability
- Easier to mandate special protections
- May allow for culturally and linguistically appropriate consent processes and forms

Group ID - Weaknesses

- Overlooks individual variations within groups
- Some may belong to more than 1 group
- Periodic or type-specific vulnerability
- Status of group may change over time
- Labeling or stigmatizing a group



12 yrs

Analytical Approach

(determines specific vulnerability characteristics)

- ***Cognitive* or *communicative*** –diminished capacity to understand
- ***Institutional*** –subject to formal authority of others
- ***Deferral*** – informal subordinate status in relation to others, e.g., cultural or societal norms; even physician and patient
- ***Medical*** – serious illness; research may be believed to be offering 'hope'
- ***Economic*** – benefits offered by research
- ***Social*** – participant groups are stereotyped therefore may subject participants to risk/benefit unacceptable to other groups.

Current Regulations

- 45 CFR 46 & 21 CFR 56 – subparts B-D
  - Subpart B – women, fetuses and neonates
  - Subpart C – prisoners
  - Subpart D – children

- State regulations
  - Illinois Surrogacy Act (755 ILCS 40/10): Decisional Capacity
  - Probate Act of 1975 (755 ILCS 5/11-1): Age of Majority

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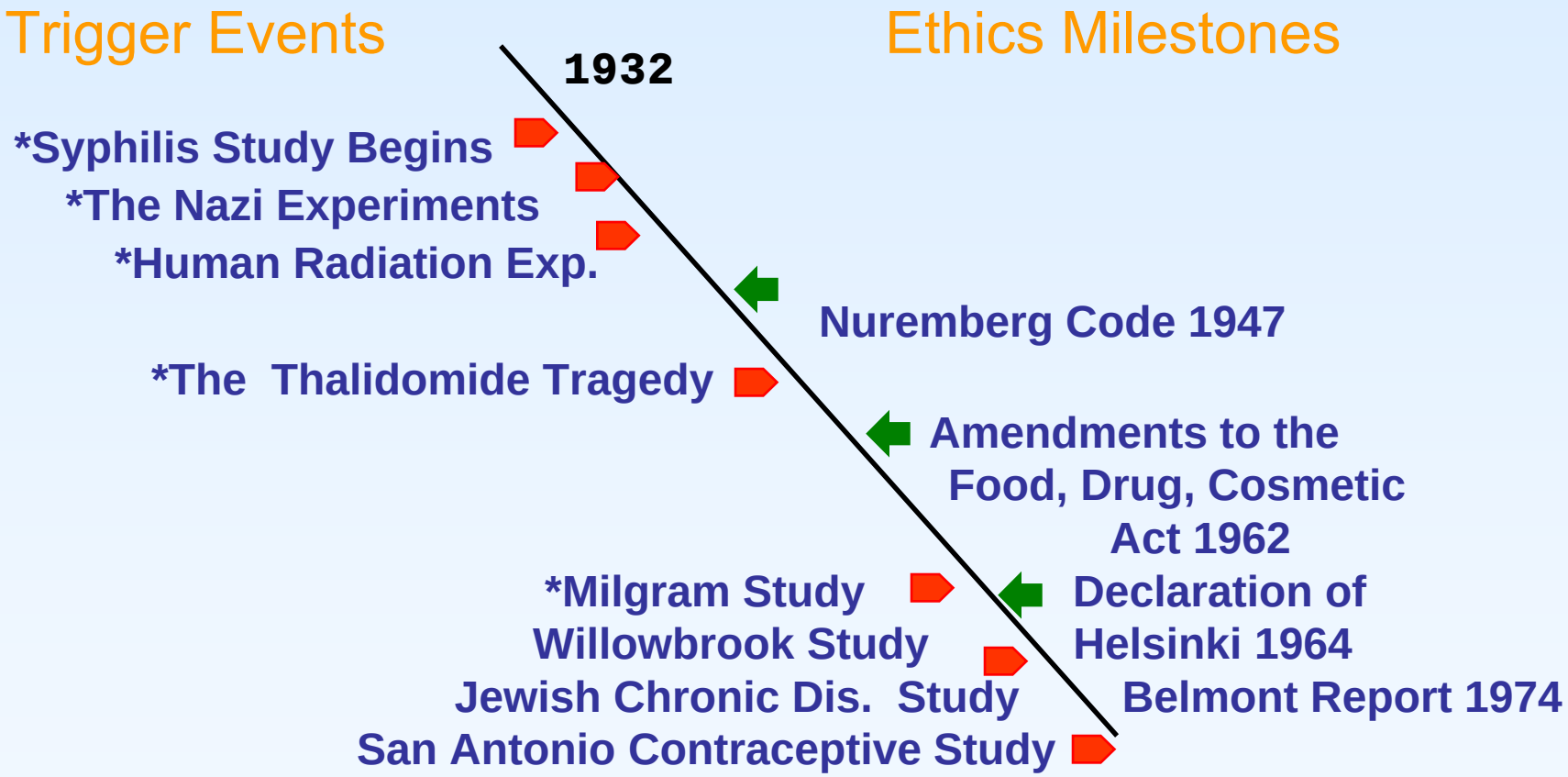
Some Historical Background for Research with Vulnerable Populations



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Tuskegee Syphilis Study

(1932-1972)


(Courtesy National Archives)

- Designed to determine the natural history of untreated latent syphilis
- Sample 399 black men with syphilis and 201 men without syphilis (controls)
- Men recruited without informed consent
- Misled regarding “special free treatment” – spinal taps
- Mortality rate twice as high in syphilis vs. non-syphilis
- When effective treatment (penicillin) became available, participants were not told – even though it was known that syphilis decreased their life expectancy by 20%
- Study continued until first accounts appeared in the press in 1972.

The New York Times

EX-CHIEF DEFENDS SYPHILIS PROJECT; Says Alabama Plan Was Not Unethical or Unscientific

New York Times. New York, N.Y.: Jul 28, 1972. pg. 29, 1 pgs

Doctor Says He Was Told Not to Treat Men in V.D. Experiment

New York Times New York, N.Y.: Aug 8, 1972. pg. 16, 1 pgs

AT LEAST 28 DIED IN SYPHILIS STUDY; Reports on Tuskegee Tests Indicate Much Higher Toll

New York Times New York, N.Y.: Sep 12, 1972. pg. 23, 1 pgs

U.S. Syphilis Study Called 'Ethically Unjustified'; Report of Tuskegee Panel to Congress Urges a Board to Guide Human Research

New York Times New York, N.Y.: Jun 13, 1973. pg. 21, 1 pgs

REGULATION URGED IN HUMAN TESTING; Panel Calls for Controls on Federally Aided Research Need for Protection Cited

By NANCY HICKS. **New York Times** New York, N.Y.: Mar 21, 1973. pg. 30, 1 pgs

Human Radiation Experiments

- In 1927, the parents of 10 African-American children at a local elementary school in Lyles Station, Indiana were approached by local healthcare officials to be treated for a fungal infection commonly called “ringworm.”
- Vertus Hardiman (d. 2007) was 5 years old when he was irradiated.
- The radiation destroyed his scalp immediately and gradually destroyed the top of his skull.
- Despite significant continuing medical complications, Hardiman led a full, productive life, and ultimately disclosed his secret to a fellow parishioner at his church.

http://my.firedoglake.com/valtin/2011/05/25/documentary-on-early-u-s-radiation-experiments-on-black-children-video-trailer/

Human Radiation Experiments

- Between April 1945 and July 1947, 18 people were injected with plutonium by doctors associated with the Manhattan Project.
- None of these men, women, and children were told what was being done, and none gave informed consent.
- Most of the subjects were the poor, powerless, or ill.
- These medical experiments were covered up for 40 years. When they became public, the government apologized but not a single doctor or hospital was publicly cited.

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The Willowbrook Studies

(1956-1971, PI: S. Krugman)

- Designed to contribute to the understanding of hepatitis and to test for the effects of gamma globulin in preventing or slowing the disease.
- Sample – children housed at the Willowbrook State School for "mentally defective persons"
- Children deliberately infected with hepatitis virus
  - Early subjects were fed extracts of stool from infected patients
  - Later, they were given an injection of purified virus
- A public outcry forced the study to end in 1971, but Willowbrook did not close until 1986.

The Willowbrook Studies Ethics

- There was parental consent for participation in the research.
- Hepatitis was common at the school before the study began.
- P.I. Krugman argued that the risk was minimal – not greater than the children's normal risk.
- Critics maintained that the parental consent letter did not mention deliberately infecting children with hepatitis.

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Jewish Chronic Disease Hospital Study

- Designed to see if delay in rejection of live cancer cells was due to debilitated nature of the patient or the presence of cancer
- Sample – 22 patients hospitalized with various chronic debilitating diseases - mostly indigent
- Purpose - acquire information regarding human transplant rejection process and immunity from cancer.
- Consent “orally negotiated”
- Patients told they were receiving a skin test
- No signed or documented consent

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Jewish Chronic Disease Hospital Study

- Research funded by U.S. Public Health Service and American Cancer Society to learn how non-cancer patients reject cancer cells, also transplant rejection
- PI: Dr. Southam (Sloan-Kettering)
- Received permission from JCDH Director, Dr. Mandel
- No review by JCDH Research Committee
- Three JCDH staff physicians objected and were ignored.

Jewish Chronic Disease Hospital Study

Outcomes

- Mandel tried to cover-up events
- Southam and Mandel claimed they did not want to scare the patients by telling them they were injecting them with live cancer cells
- They thought the cells would be rejected
- Felt consent not necessary because more serious procedures were commonly done without consent
- Lumps at injection sites disappeared seven weeks after injections

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Jewish Chronic Disease Hospital Study

Outcomes

- Board of Regents suspended Southam and Mandel, later changed to 1 year probation
- No sanctions for Sloan-Kettering, JCDH, USPHS or ACS
- Led to development of federal guidelines to protect research subjects
- Southam had done similar experiments to prisoners in 1952 at Ohio State Prison
- Southam was later elected vice-president of ACS

Jewish Chronic Disease Hospital Study

How they might have justified the study:

- Deontological—Southam and Mandel believed that what they were doing was right according to laws of the time.
- Consequentialism—they believed the study would generate valuable medical information.
- Virtue ethics—they believed they were in the right , because of their good intentions: To generate insight into cell behavior.

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Jewish Chronic Disease Hospital Study

Using the principles of the Belmont Report:

- Respect for Persons
  - Autonomy : participants should be given choices, have their opinions heard, volunteer for the research without pressure to participate, and be given ample time to decide.
  - In this case, none of these safeguards were observed.

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Jewish Chronic Disease Hospital Study

Using the principles of the Belmont Report:

- Respect for Persons
  - Persons with diminished autonomy require additional protections
  - Patients were elderly, debilitated, indigent
  - Staff physicians objected on the grounds that patients were incapable of giving adequate consent.
  - If the rules of informed consent were followed, this study would have not have occurred.

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Jewish Chronic Disease Hospital Study

Using the principles of the Belmont Report:

- Benificence
  - Balance of risk & benefits
  - Maximizing benefits while minimizing harm
  - In this case, even if consent was given, the potential harm of injecting live cancer cells would have to be balanced with the benefits of the knowledge gained.
  - This would likely require wide-scale changes to this experiment.

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Jewish Chronic Disease Hospital Study

Using the principles of the Belmont Report:

- Justice
  - Who should bear the risks vs. who receives the benefits
  - Participants should be included for reasons of the study, not because of availability, compromised position, or vulnerability
  - Patients in this study were both vulnerable and in a compromised position—following this principle they would have had to use a different, not just a convenient population

San Antonio Contraceptive Study (1969)

- Designed to determine which of the side effects of an oral contraceptive were due to the drug and which "reflect[ed] the symptomatology of everyday life"
- Sample – impoverished Mexican-American women previously having multiple pregnancies coming to the clinic for contraceptives
- Study was randomized, placebo-controlled, double-blind clinical trial with a cross-over design
- None of the women were told there was a placebo involved as part of the study

The Thalidomide Tragedy

- Invented by Heinrich Mückter, a former NSDAP member and German army physician.
- Launched by Grünenthal on 1 October 1957.
- Inhibited morning sickness.
- FDA never licensed thalidomide, BUT
- 20,000 pregnant women in the US received thalidomide as part of a clinical trial conducted by Merrell Pharmaceuticals

The Thalidomide Tragedy

- Thalidomide was also included in some 50 OTC drugs to relieve colds and flu and morning sickness.
- It was not believed that drugs taken by the mother could cross the placental barrier, so Merrell did not collect data on birth defects.
- By 1961, reports reached the FDA that thalidomide might be associated with birth defects. FDA refuses license.
- In 1962, FDA pharmacologist Frances Oldham Kelsey received a Presidential commendation for refusing to license thalidomide.

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The Milgram Experiments

Public Announcement

WE WILL PAY YOU $4.00 FOR ONE HOUR OF YOUR TIME

Persons Needed for a Study of Memory

*We will pay five hundred New Haven men to help us complete a scientific study of memory and learning. The study is being done at Yale University.

*Each person who participates will be paid $4.00 (plus 50c carfare) for approximately 1 hour's time. We need you for only one hour: there are no further obligations. You may choose the time you would like to come (evenings, weekdays, or weekends).

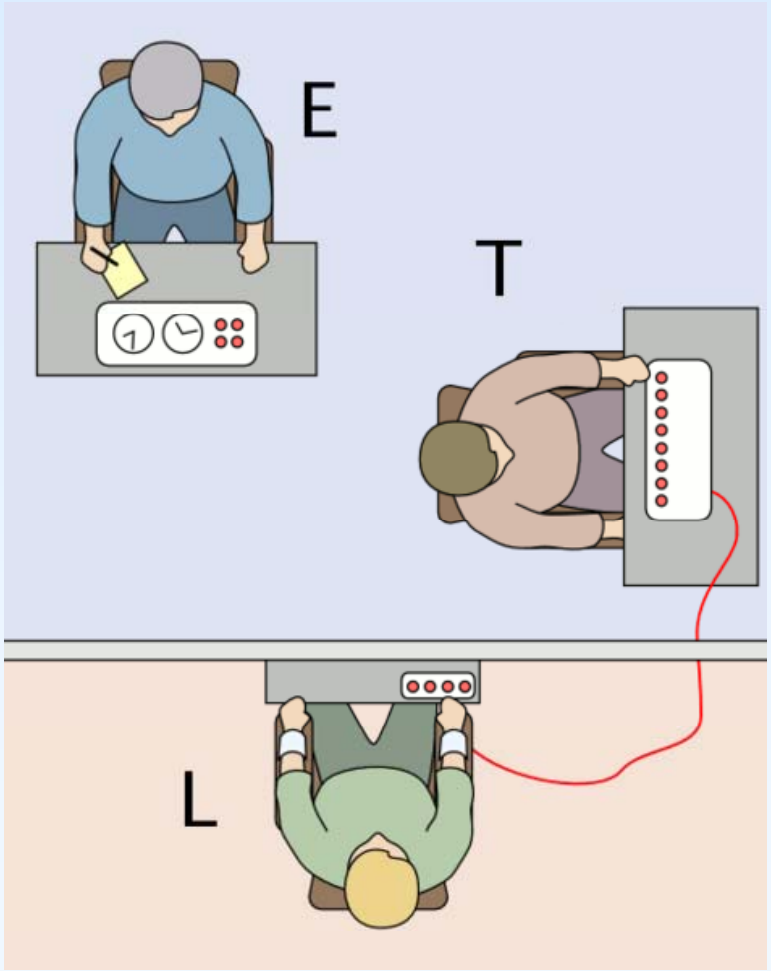
***No special training, education, or experience is needed. We want:**

Factory workers	Businessmen	Construction workers
City employees	Clerks	Salespeople
Laborers	Professional people	White-collar workers
Barbers	Telephone workers	Others

All persons must be between the ages of 20 and 50. High school and college students cannot be used.

*If you meet these qualifications, fill out the coupon below and mail it now to Professor Stanley Milgram, Department of Psychology, Yale University, New Haven. You will be notified later of the specific time and place of the study. We reserve the right to decline any application.

*You will be paid $4.00 (plus 50c carfare) as soon as you arrive at the laboratory.



The Milgram Experiments

- What vulnerable population was involved in the Milgram Experiments?
- What other individual vulnerability did the Milgram Experiments exploit?
- What ethical principles did the Milgram Experiments violate?
- Should a research project be judged unethical if we don't like what it tells us about ourselves?

Ethics and the Milgram Experiments

- The Milgram experiments subjected participants to emotional stress, and unpleasant insights.
- “The question arises as to whether there is any connection between what we have studied in the laboratory and the forms of obedience we so deplored in the Nazi epoch.” (Milgram, 1974, p. xii)
- When surveyed later 84% of participants said they were “glad” or “very glad” to have participated, 15% chose a neutral response, and 1% negatively evaluated their participation (92% responded).

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Ethics as penance? The case of Henry K. Beecher

The New England Journal of Medicine

Copyright, 1966 by the Massachusetts Medical Society

Volume 274 JUNE 16, 1966 Number 24

Reprinted from pages 1354-1360.

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON

Henry K. Beecher

- Beecher's 1966 article drew attention to 22 examples of unethical clinical research that had risked patients' lives.
- He was severely criticized by the medical establishment for what was felt as an unfair generalization from a few select cases.
- This article laid the foundation for current guidelines on informed consent and human experimentation.

Henry K. Beecher

- Beecher was scientifically responsible for human experiments in a secret CIA-prison related to the nearby US-interrogation center Camp King (West Germany).
- Several interrogated individuals died. This report states that since September 1951, Beecher prepared human experiments with various drugs.
- Several times he allegedly met with former Nazi-physician Walter Schreiber for an "exchange of ideas". Later Beecher described Schreiber in a report as *"intelligent and cooperative."*

Vulnerable Populations

Why are children vulnerable?

- Developmental age – lack of ability to understand concepts
  - At what age can children comprehend abstract thinking?
- Under authority of others (e.g., parents, teachers)
- Easily coerced

Children

Regulations:

- 45 CFR 46 – Subparts A & D
- 21 CFR 50 & 56

- NIH Policy & Guidelines on the Inclusion of Children as Participants in Research
- OHRP – Special Protections for Children as Research Subjects

Permission or Consent?

Permission

- Asks for parental permission to allow child to participate in research

  THEN

- Assent
  - "A child's affirmative agreement to participate in research"….."Failure to object, absent affirmative agreement, should not be construed as assent." (45 CFR 46.402(b))

Consent

- Having 'capacity' to agree for one's self to participate in a given situation, e.g., research
- Understands risks and benefits of participation and agrees to potential consequences

Illinois State Law

- Age of majority – 18
- Emancipation
  - age 16 or 17 if no parental objection
  - Living apart from parent
  - Self supporting
- Mature minor
  - Contracts by Minors
  - Consent for medical treatment if married, a parent, or victim of sexual assault.

- Common Law
- §§750 ILCS 30/1, et seq.
- Executed contract binding unless disaffirmed within reasonable time after age 18; common law
- Consent by minor if married, parent, or victim of sexual assault (410 ILCS 210/1, et seq.)

Ethical Considerations in Obtaining Parental Permission for a Minor's Participation

- Level of parental duress
- Research incentives
- Parental perception of physician-parent relationship
- Child's thoughts and considerations

Disability/Handicapped

Mental Disability

- Psychiatric disorder or developmental disorder affecting cognitive, emotional functions (decreased capacity)
- May lack ability to understand (reasoned decision)
- Surrogate consent
  - If benefit present
  - No more than minimal risk
- Assent

Regulations

- IRB regularly reviewing research involving vulnerable category of subjects, e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons, should include one or more individuals with knowledge and experienced in working with these subjects.
- Risks to subjects are:
  - Minimized and
  - Reasonable in relation to anticipated benefits
- Selection of subjects is equitable.
  - IRB should take into account
    - **the purposes of the research,**
    - **the setting in which the research will be conducted,**
    - **special problems of research involving vulnerable populations**

Consent Issues

- Best Interests Standard
  - Norm to guide moral, social and legal decisions
  - Seeks to maximize benefits and minimize harm
  - Much confusion due to multiple interpretations
- Substituted Judgment Standard
  - Used when an individual is deemed incapable of acting on his/her own behalf

Ethical Considerations

- Consider:
  - Permanent or temporary impairment
  - Is research integral to persons with mental impairments?
  - Does the IRB of record have members specifically qualified for this population?

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Prisoners in Research

- Prisoner – individual involuntarily held or detained in a penal institution
- For DHHS funded studies:
  - Institution must be certified
  - Research must fall under specific categories
    - Cause & effect of incarceration
    - Prisons as institutional structures or prisoners as incarcerated persons w/no more than minimal risk
    - Particular conditions/diseases affecting prisoners*
    - Having reasonable probability of prisoner benefit * *
- IRB must have a prisoner or prisoner representative (e.g., chaplain)

45 CFR 46 - Subpart C

- At least one member of the Board shall be a prisoner, or a prisoner representative
- No coercion
- No imbalance in the risk/benefit
- Participant selection is fair
- Research is directly related to prison environment
- 2003 – added ability to conduct epidemiologic research

Consent Issues

- Terminology must be understandable
- No special treatment for study participation
- Parole board cannot consider study participation when determining parole

Ethical Issues

- Prisoners are under the influence of others
- Can prisoners exercise free power of choice or consent?
- Is it coercion or bribery?

Pregnancy

- Pregnancy places a woman in a vulnerable category when the state her body is in places her at higher risk – disruption of balance of risk to benefit

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§46.204

- Preclinical data identifying risks required where appropriate
- Least possible risk to achieve research objective(s)
- Fully informed participants
- No inducements to terminate pregnancy
- Researchers have no part in:
  - Decisions to terminate pregnancy
  - Determining viability

Consent Issues

- Consent of pregnant woman if direct benefit to her or risk to fetus is not greater than minimal
- Consent of pregnant woman **AND** father if research offers direct benefit solely to fetus
- Pregnant children – assent and permission per Subpart D

Handicapped

- How to relate issues to 'physically disabled?'

"In many industrialized countries, the obsession with independence devalues people with disabilities, who are believed to personify weakness or vulnerability." *Jennifer Kern*

Regulations

- IRB regularly reviewing research involving vulnerable category of subjects, e.g., children, prisoners, pregnant women, or *handicapped* or mentally disabled persons, should include one or more individuals with knowledge and experienced in working with these subjects.

Consent Issues

- Issues would arise based on how physical handicap affects capacity

Institutionalized

- Research related to institutionalized individuals is important
  - Determine that institutionalization increases risk to the population

Consent Issues

- Capacity
- Surrogate – without benefit from research

Ethical Issues

- How to determine capacity
- How to determine if study participation effects individual's care

Terminal Illness

- Vulnerability may exist if the patient looks to research as last effort of hope.
- Consent issues – potential for capacity loss; possible influence of others
- Ethical issues
  - fully informed consent;
  - honesty

Vulnerability: Questions to ponder

- If you are vulnerable once – are you vulnerable forever?
- When is a child not a child?
- Are emotionally disabled persons always vulnerable?
- Where does vulnerability start and stop?
- Do justice, beneficence, and respect for persons ever conflict?

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Research on Research on Vulnerable Populations

Study 1: Persons with Intellectual Disabilities in Research

- MacDonald, Keys, & Henry (2008)
  - Sample:
    - 116 IRB members
    - 114 intellectual disabilities researchers
    - 30 were both
  - 55.4% female
  - 84.6% had close to very close relationships with persons who had intellectual disabilities.

Persons with Intellectual Disabilities in Research

Administered Questionnaire on General Attitudes

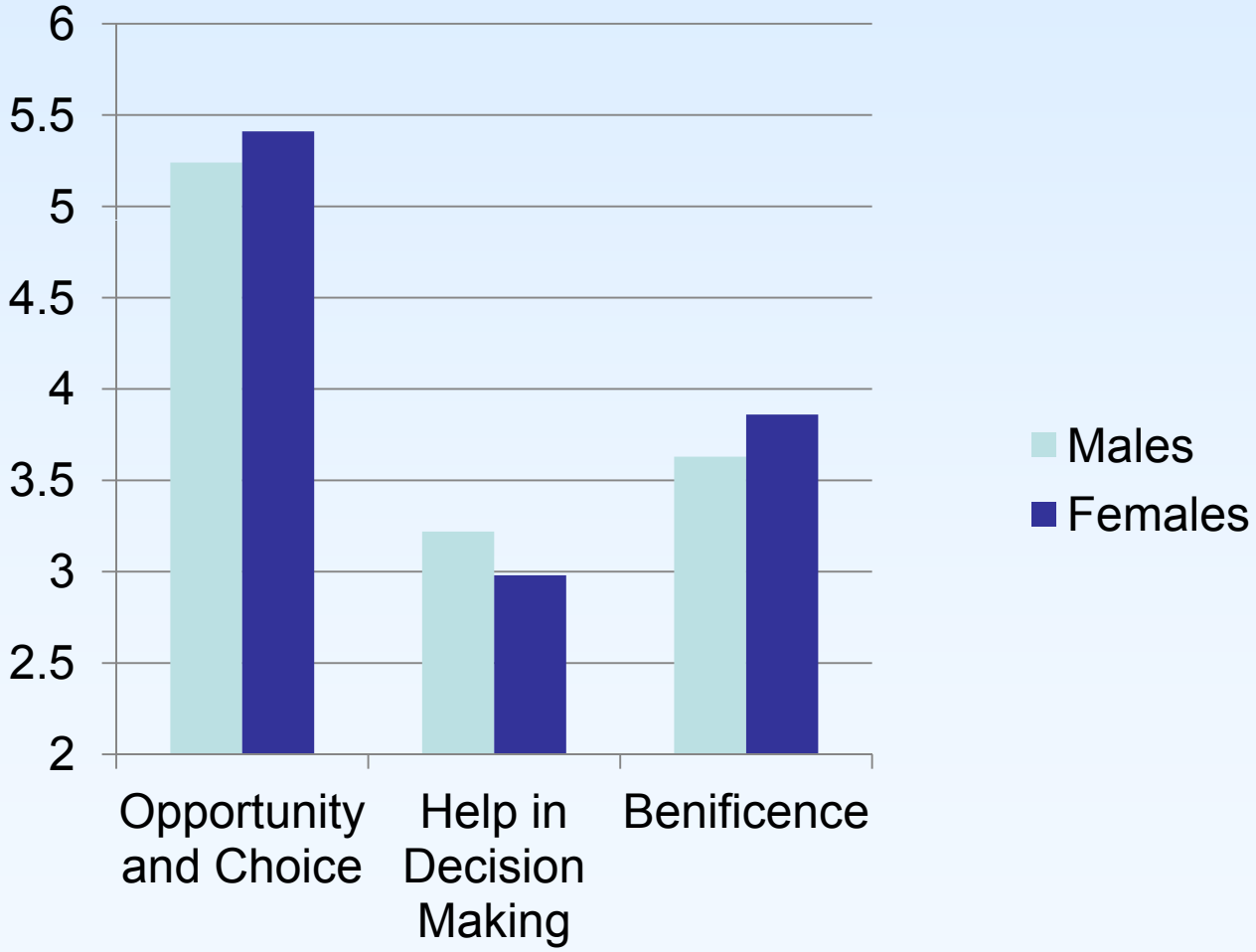
- *Empowerment*, e.g., “People with ID can be trusted to handle money responsibly..”
- *Exclusion*, e.g., “People with ID are a burden on society.”
- *Sheltering*, e.g., “People with ID usually should be in group homes or other facilities where they can have the help and support of staff.”
- *Similarity*, e.g., “People with ID have goals for their lives like other people.”

Persons with Intellectual Disabilities in Research

Developed Questionnaire on Specific Attitudes

- *Opportunity and Choice* (α=.86), e.g., "People with ID want the choice to participate in research."
- *Help in Decision Making* (α=.84), e.g., "People with ID can provide consent to participate in research as well as anybody else."
- *Benificence* (α=.70), e.g., "People with ID should only participate in research when the personal benefits outweigh the potential harm."

Persons with Intellectual Disabilities in Research



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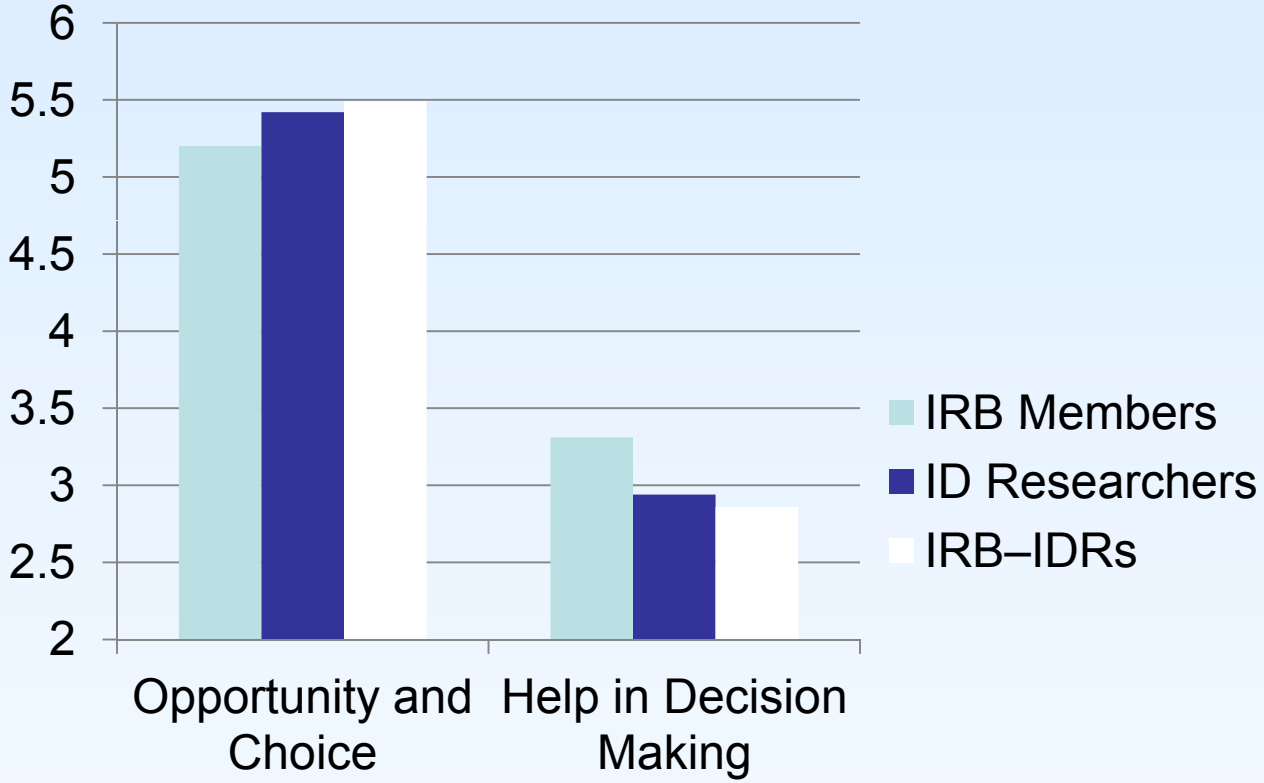
Persons with Intellectual Disabilities in Research



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Persons with Intellectual Disabilities in Research

Study 2: Enrolling decisionally impaired adults without direct benefit

- Karlawish, Rubright, Casarett, Cary, Ten Have, & Sankar (2009, AJP) presented 538 adults aged 65 and older with scenarios in which patients with Alzheimer's Disease were enrolled in a study involving either a blood draw (minimal risk) or a blood draw plus a lumbar puncture (greater than minimal risk).
- They were asked about providing advance consent for such a study or consent via a proxy decision.
- Other questions assessed altruism, trust of health professionals and value of research.

Enrolling decisionally impaired adults without direct benefit

- 83% were willing to grant advance permission for a blood draw study, and nearly half (48%) were willing to grant advance permission for a study involving a blood draw plus a lumbar puncture.
- 96% were willing to appoint a proxy for research consent, and to grant the proxy leeway to decide on the blood draw (81%) and the blood draw plus lumbar puncture (70%) studies.

Enrolling decisionally impaired adults without direct benefit

- Taking advance and proxy consent together, a total of 92% were willing to participate in the blood draw study and 75% in the blood draw plus lumbar puncture study.
- Whites were less likely than minorities to grant advance consent for the greater than minimal risk study.
- Those with a higher sense of social responsibility, greater trust of health professionals, and more positive attitudes about research were more likely to consent to either study.

Questions?

Part 2
Considerations from the UIC Institutional Review Board on Research with Special Populations

Initial Review Application, XIII

B. Age Range (check all that apply):

☐ Newborn to 17 years of age* - *Complete Appendix B if the research involves children*
☐ 18 - 64 Years

C. Indicate which populations below are the PRIMARY FOCUS of this research. Remember to take into account the location in which recruitment will occur and where the research will be conducted. Also note that additional information and/or safeguards will be required, as indicated below, when a subject population has been designated as vulnerable (with an asterisk *).

Check all that apply

☐ Adults: Healthy Subjects or Control Subjects
☐ Adults: Patient Subjects
☐ Pregnant Women, Neonates, Fetuses/Fetal Tissue – *Appendix U must be included* *
☐ Prisoners – *Appendix C must be included**
☐ UIC Employees*
☐ UIC Students*
☐ UIC Psychology Student Subject Pool* - *please see OPRS or Psychology Department website for policy*
☐ Decisionally Impaired* - *Appendix V must be included* *
☐ Economically and/or Educationally Disadvantaged*
☐ Vulnerable to Coercion or Undue Influence*
☐ JBVAMC
☐ Other: specify

D. Please note the groups listed directly above marked with an asterisk (*), as well as subjects under the age of 18, are considered "vulnerable" and require special consideration by the federal regulatory agencies and/or by the UIC IRB. If vulnerable populations will be recruited as subjects, **the appropriate Appendixes (indicated above) must be attached to this application. Illinois State Law does not allow prisoners to participate in biomedical research.** Provide a rationale and justification for the inclusion of each vulnerable population indicated above as a primary focus of the research.

Operational Definitions

- HUMAN SUBJECT
  - A living individual from whom the investigator of the research project obtains information (i.e., data) [1]
- RESEARCH
  - Any systematic investigation that has the goal of contributing to any generalizable knowledge or scientific database [1]

Guidelines for “Special Populations”

- The UIC IRB has specific guidelines issued for 6 special populations
  - Children (including wards of the state)
  - The decisionally and cognitively impaired
  - Pregnant women, human fetuses and neonates, and fetal tissue
  - Prisoners
  - Persons who do not speak English
  - Other populations
- What happens if a subject has membership to more than one special population?

Children

Key Definitions

- Assent: A child's affirmative agreement to participate in research
- Child/children/minors: An individual under the age of 18 years old
- Foster child: A ward of the state held by the Illinois Department of Children and Family Services
- Guardian: An individual is authorized to consent on behalf of a child to general medical care

Circumstances When Minors Can Consent for Themselves

- Emancipated or Mature Minor
- Special situations
  - Married
  - Parent
  - Pregnant

Other IRB Considerations

- When assent is required by the IRB, the decision of the child assenting is binding, provided parental or guardian permission, when necessary, has been obtained
- When the durations of the child's participation may continue beyond the age of majority, the investigator must include provisions for the now-adult's continued participation
- All potential geographical and jurisdictional IRB considerations must be accounted for.

Classification

- In order to provide additional safeguards, children are classified into one of four categories based on the risk-benefit profile
- For these categories, “minimal risk” means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in **daily life** or during the performance of **routine** physical or psychological examinations or tests.

Classification

- Category 1: Research not involving greater than minimal risk (one parent permission required) **§46.404**
- Category 2: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child (one parent permission required) **§46.405**
- Category 3: Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition (two parent permission required) **§46.406**
- Category 4: Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (two parent permission required) **§46.407**

Obtaining Child Assent

- The IRB generally requires assent for children aged 7 years and older
- Is the child capable of providing assent?
  - Age?
  - Maturity?
  - Psychological state?
- The assent should provide the child with an age-appropriate explanation of the proposed research procedures (explanation of activities, duration of research etc.)
- Age and assent
  - Aged 7-12: No longer than 1-page assent
  - Age > 12: Similar to adult assent
- In some special situations, the IRB reserves the right to waive child assent.

Investigator Responsibilities

- Any changes in the legally authorized representative status of the child
  - Routine assessment with the accompanying guardian
  - Informed consent for the guardian regarding guardianship status
- Wards of the state
  - Particular care with wards (e.g., if ward gets adopted)
  - Additional precautions

Persons who are Decisionally and/or Cognitively Impaired

Key Definitions

- Cognitively impaired: Having either a psychiatric disorder, an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished
- Competence: Ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice
- Decisional capacity: The ability to understand and appreciate the nature and consequences of a decision regarding medical treatment and the ability to reach and communicate an informed decision in the matter
- Incapacity/incompetent: Inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice

IRB Approval

- Adherence to any state laws regarding research with persons unable to consent for themselves
- **Research involved should be relevant to subject's condition or circumstances**
- PI must propose adequate procedures for evaluation of mental status
- Risk-benefit consideration
- IRB must consider…
  - Required assent
  - Required advocate or consent auditor
  - Interference with current therapy
  - Consultation with subject's physician
  - Fluctuating capacity

Role of the LAR

- In general, consent is provided by the subject's legally authorized representative (LAR). Assent is taken from the subject.
- The IRB ensures the LAR is given a description of the study, and is well-informed of the his or her obligation of protecting the subject
- In order to seek consent from the LAR, the PI must obtain a copy of documents certifying that the subject is unable to make decisions

Illinois Surrogacy Act

Surrogate Decision-makers for Medical Treatment:

- the patient's guardian of the person;
- the patient's spouse;
- any adult son or daughter of the patient;
- either parent of the patient;
- any adult brother or sister of the patient;
- any adult grandchild of the patient;
- a close friend of the patient;
- the patient's guardian of the estate.

Risk-benefit Considerations

- IRB must consider a subject's ability to provide consent and to withdraw from the study
  - Ability to make a choice
  - Ability to understand relevant information
  - Ability to appreciate the situation and its likely consequences
  - Ability to think through information rationally
- The research should not pose a harm, unless the probability of benefit is greater than probability of harm
- Levels of consideration
  - No more than minimal risk
  - Greater than minimal risk but direct benefit
  - Greater than minimal risk and limited to indirect benefit

Pregnant women, human fetuses and neonates, and fetal tissue

Key Definitions

- Dead fetus: A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord
- Delivery: A complete separation of the fetus from the woman by expulsion or extraction or any other means
- Fetus: The product of conception from implantation until delivery.
- Neonate: A newborn
- Nonviable neonate: A neonate after delivery that, although living, is not viable
- Pregnancy: The period of time from implantation until delivery. A woman is assumed to be pregnant if she exhibits any of the pertinent signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery
- Viable: As it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration

Consent of a Pregnant Minor

- Under Illinois law, a pregnant minor may provide her own consent to the performance of a medical or surgical procedure if performed by:
  - A physician licensed to practice medicine and surgery
  - An advanced practice nurse who has a written collaborative agreement with a collaborating physician that authorizes provision of services for minors or
  - A physician assistant who has been delegated authority to provide services for minors.

Subgroups of Studies identified by the IRB

- Studies in which pregnancy is coincidental to subject selection
- Research involving pregnant women or fetuses
- Research involving neonates
- Research involving, after delivery, the placenta, the dead fetus or fetal material

Studies in Which Pregnancy is Coincidental to Subject Selection

- When the research population may include women of child bearing potential, the possibility exists for the inadvertent inclusion of pregnant women
- However, the IRB may take the following factors into account:
  - Is it appropriate to highlight potential risk to pregnancy in the informed consent?
  - Does the mother's involvement pose any risk to the fetus or nursing infant?
  - Should non-pregnant participants be advised to avoid pregnancy or nursing during the study period?
  - Is there a need to advise participant to immediately contact the investigator should they become pregnant?

Research Involving Pregnant Women or Fetuses

- 2 primary considerations of the IRB
  - Whether the research is directed to the mothers' or fetus' health
  - The risk to the woman and the fetus
- The following conditions must be met for pregnant women or fetuses to be involved with research:
  - Animal and non-pregnant studies have indicated safety
  - Favorable risk-benefit profile
  - No inducements, monetary or otherwise, will be offered to terminate pregnancy
  - Individuals engaged in research will have no part in the decision making of terminating pregnancy or determining viability
  - Any risk is the least possible for achieving the research objectives
  - Consent of the mother **and** father is obtained

Research Involving Neonates

- Differ by degree of viability
  - Neonates of uncertain viability
  - Nonviable neonates
  - Viable neonates
- Generally, IRB restrictions increase as prospect for survival decreases

Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

- Research must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities, which may include the Illinois Anatomical Gift Act

Research Involving Prisoners

Key Definitions

- Prisoner: Any individual involuntarily confined or detained in a penal system institution
  - Individuals in prison, jail, or juvenile offender facility
  - Individuals detained in a residential facility for court-ordered substance abuse treatment
  - Individuals committed involuntarily due to psychiatric illness as an alternative to criminal incarceration
  - Parolees who are detained in a treatment center as a condition of their parole
- Minimal risk: The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of health persons

Limitations of Intervention

- Medical, cosmetic, or pharmaceutical experiments involving prisoners are prohibited for research to be conducted within the Illinois Department of Corrections

IRB Approval

- To obtain approval…
  - Any possible advantages accruing to the prisoner for participation should not be great enough to impair his or her judgment
  - The risks involved in the research are commensurate with the risks that would be accepted by non-prisoner volunteers
  - Procedures for the selection of participants are fair to all prisoners, unless the investigator provides justification for the enrollment of a specified prison sub-group
  - The information is presented in a language which is understandable to the participants
  - Assurance that participation in the study will in no way influence a parolees status
  - Adequate provisions have made for a prisoner's incarceration status at follow-up

Categories of Research

- Studies of the possible causes, effects, and processes of incarceration
- Study of prisons as institutional structures or of prisoners as incarcerated persons
- Research on conditions particularly affecting prisoners as a class
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health and well-being of the participant
- Research to describe the prevalence and incidence of a disease by identifying all cases, or to describe potential risk factor associations for a disease (*Federal Register 68 36929, June 20,* 2003)

Membership Requirements

- A majority of the Board must have no association with the prison involved
- At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity (e.g., prison chaplains, prison psychologists, prison social workers, other prison service providers, or persons who have conducted advocacy for the rights of prisoners)

Measures if a Current Subject Becomes a Prisoner

- The investigator is responsible for reporting the event in writing to the IRB within 10 working days
- If the subject continues participation, an amendment must submitted to the IRB
- Until these measures are taken, the obtaining of identifiable private information must cease

Non-English Speakers

Requirements for Investigators

- UIC investigators are required…
  - To provide an ethical and scientific justification for excluding subjects who can not understand or read English, but otherwise are eligible to participate, from a research proposal
  - To include non-English speaking subjects in research, particularly when the research offers the subject the potential for direct benefit, unless the UIC IRB reviews and approves the investigator's justification for exclusion

Methods for Obtaining Informed Consent

- Method 1: Written translation of IRB-approved English informed consent
- Method 2: Short form consent process

Written Translation of IRB-approved English Informed Consent

- Translations of the informed consent documents must be reviewed and approved by the IRB (recommended to be submitted as an amendment following approval of English language informed consent)
- A back-translation of the consent document(s) to check for accuracy should be done
- If a member of the research team is not fluent in the subject's language, a translator fluent in English and the subject's language should be used
- If a translator is present, he or she should also sign the informed consent document
- A plan of future communication with the subject should be provided to the IRB

Short form consent process

- The short form is a document written in language understandable to the subject stating that the elements of informed consent, which are outlines on the form in general terms, have been presented orally and understood by the subject, or their LAR
- A translator fluent in English and the subject's language must read the consent summary to the subject in their language
- A witness to the oral presentation should be present
- A plan of future communication with the subject should be provided to the IRB

Other Populations

Other Populations

- Any groups who “are at risk for coercion and undue influence”
  - Terminally ill persons
  - Economically disadvantaged persons
  - Educationally disadvantaged persons

Final Notes

- The guidelines described by the UIC IRB “special populations” are in place for the protection of human subjects, specifically groups that are vulnerable to coercion
- Understanding of the language and strong vigilance are required for investigators to properly adhere to IRB mandates
- The full documents used herein can be found at the UIC Office for the Protection of Research Subjects website at:

http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/