Yale *Human Research Protection Program*

Vulnerable Populations

Theresa Katz, CIP

Griselle Gandulla, MS CIP

Yale *Human Research Protection Program*

Training Agenda

Agenda Item	Slide #s
Introduction	N/A
Learning Objectives	3
Sub-Parts A and D: Children	4-17
Sub-Part B: Pregnant Women and Fetuses	18-29
Sub-Part C: Prisoners	30-40
Cognitive Impaired Participants	41-51
Summary	52-53
Resources	54
Closing Statements	N/A

Learning Objectives

- Identify the vulnerable populations under 45CFR46 Sub-Parts A, B, C, and D.
- Understand the IRB pre-review and review process for working with various groups of vulnerable populations in research.
- Examine why it is crucial to include these groups in research.
- Review ethical frameworks and guidelines that govern research involving these populations.
- Identify practical approaches to ethically include vulnerable populations in research while ensuring their protection.

Yale *Human Research Protection Program*

Children in Research

Yale *Human Research Protection Program*

Children in Research

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.402(a)]. Emancipated minors are considered adults for the purpose of this policy.

Guardian: a guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care [45 CFR 46.402(e)].

Children in Research

Infant or infancy: is generally considered to be the period from birth until age 2 years. It is a time of rapid growth and change for children and families.

Adolescent or adolescence: period of significant development that begins with the onset of puberty[1] and ends in the mid-20s.

https://www.nichd.nih.gov/health/topics/infantcare/conditioninfo
Adolescent Development - The Promise of Adolescence - NCBI Bookshelf

Children in Research

According to Connecticut (CT) State Law, minors are persons under the age of eighteen. The general rule is that a person may sign legally-binding agreements and consent for his or her own medical care at the age of eighteen. Therefore, Yale IRB defines children as persons who are under eighteen years of age. Because CT law does not specifically address consent of children with majority status to research, Yale IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

Children in Research

History:

- Published for the first time in 1983 by the Department of Health and Human Services.

- Subpart D: parents must, under most circumstances, provide permission before children (usually those under age 18 as defined by state laws) can participate in research. It also provides that, when appropriate, children should affirmatively agree or assent to participate in research.

- They defer to state laws that define both the age at which individuals become entitled to make medical care decisions and the special circumstances under which minors may make such decisions in their own right (e.g., for care related to sexual health).

Children in Research

Challenges in the recruitment of children

- Complexity of parental involvement and family decision making.
- Need to accommodate the child's physical, cognitive and emotional needs.
- Need to develop appropriate outcomes for children of different ages.
- Developmental variability.
- Commercial value: smaller market specially for rare diseases.
- Widespread off label use of medications.
- Culture

Children in Research

How to overcome barriers for the recruitment of children in research:

- Offer reimbursement for reasonable expenses.
- Compensate parents for lost wages or time.
- Adjust time or places for research visits to avoid taking time off work or school.
- Design longitudinal studies.

Children in Research

Historical Unethical Studies involving Children:

-**Josef Mengele twin studies**: Twins aged 2-16 years old received weekly examination and measurements, then they were separated. One was experimented on and another one acted as a control for his/her twin.

-**Sonoma State Hospital**: Children underwent experimentation without parental permission, for which there was no direct benefit.

-**Willowbrook study**: Children were infected with Hepatitis and not treated.

-**National Children Study**: NIH longitudinal study that collapsed without generating much needed data.

Children in Research

OHRP Regulations:

- 45CFR 46.404: Research not involving greater than minimal risk to the children.

- 45CFR 46.405: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

- 45CFR 46.406: Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.

Children in Research

OHRP Regulations (continued):

- 45CFR 46.407: Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

- 45CFR 46.409: Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:
  1. Related to their status as wards; or
  2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

Children in Research

Consent/Assent Requirements

Risk level	**Assent** *(Determined by the IRB and may vary based on age, maturity, and psychological state of the child)*	**Parental Permission**
45CFR 46.404	Yes	Yes, one parent
45CFR 46.405	Yes	Yes, one or two parents based on IRB determination
45CFR 46.406	Yes	Yes, two parents
45CFR 46.407	Yes	Yes, two parents plus OHRP Secretary approval

Children in Research

Consent/Assent Requirements:

- Unless waived by the IRB:
  - Assent (either verbal or written depending on the child population) is generally required for children ages 7 years old and up. The IRB is responsible for determining that adequate provisions are made for soliciting the assent of children, when in the judgment of the IRB the children are capable of providing assent.
  - Parental permission is required. The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.
  - Reconsent of children when they reach the age of majority (18-year-old) is also required if the children (or their data/specimens) will continue to be enrolled/analyzed.

Children in Research: Considerations

Considerations:

- Reaching age of maturity.
- How will I get assent?
- Are the procedures the same for all age groups?
- How will I get parental permission?
- Pregnancy in minors.
- Research in schools is also governed by FERPA and PPRA.
- We are all mandated reporters.

Children in Research: Considerations

Key Takeaways:

1. Successful research activities with children are possible.

2. Be creative with schedules: dates/times/places/consent & assent forms.

3. Understand the regulations, they were designed to protect children and help researchers.

4. When in doubt always contact the IRB for assistance.

Yale *Human Research Protection Program*

Pregnant Women

Yale *Human Research Protection Program*

Importance of Including Pregnant Women

- Pregnant women often use medically necessary drugs without a clear scientific understanding of the risks and benefits to themselves or their developing fetuses.
- This lack of data is primarily due to the exclusion of pregnant women from clinical trials because of the ethical dilemmas involved.
- Pregnant women are considered vulnerable because the implications of research can affect both the mother and the unborn child, adding layers of ethical and medical complexity.
- Today, we'll explore how we can balance the need for research with the protection of vulnerable populations.
- Source: FDA's Guidance on Pregnant Women in Clinical Trials

Ethical Challenges and Considerations

- Informed consent complexities.
- Risk versus benefit analysis.
- Maintaining autonomy and dignity.

Ethical Challenges and Considerations

Informed consent complexities –

- Understanding and Communication: *Pregnant women may face heightened emotional stress and cognitive overload.*

- Dual Consent: *Pregnancy involves two interconnected lives, the mother and the fetus. Any research affecting a fetus also impacts the mother's health and vice versa.*

- Potential Coercion: *Vulnerable populations may feel coerced into participating in research due to their circumstances.*

Ethical Challenges and Considerations

Risk versus Benefit Analysis –

- Risk Minimization: *Ethical research involving pregnant women requires careful minimization of risk to both the mother and the fetus.*

- Direct Benefit: *Research involving pregnant women should ideally offer a prospect of direct benefit to this population.*

- Balancing Competing Interests: *The interests of the pregnant woman and her fetus may not always align.*

Ethical Challenges and Considerations

Maintaining Autonomy and Dignity –

- Respecting Decisions: *Pregnant women must be allowed to make their own informed choices about participating in research without pressure or undue influence.*
- Cultural Sensitivity: *Autonomy involves recognizing and respecting cultural, social, and personal beliefs.*
- Ensuring Privacy and Confidentiality: *Protecting the privacy and confidentiality of pregnant women in research is paramount.*
- Support Systems: *Providing support systems during and after the study can help maintain the dignity and well-being of participants.*

Historical Context and Present-Day Challenges

Historical Context –

- Thalidomide Tragedy (1960s): *This catastrophic event, where a medication caused severe birth defects, led to significant changes in drug testing and regulations, and reshaped the approach to enrolling pregnant women in research.*

- DES (Diethylstilbestrol) Crisis (1970s): *The DES Crisis refers to the widespread discovery of health problems in the 1970s among the children of women who took the synthetic estrogen DES during pregnancy between 1940 and 1971.*

- Exclusion of Women in Research (Post-1970s): *Historically, women were excluded from research for several reasons.*

Historical Context and Present-Day Challenges

Present-Day Challenges –

- Healthcare Needs: *Pregnant women still require medications and interventions for health conditions unrelated to pregnancy.*
- Regulatory and Ethical Tensions: *The ethical imperative to "do no harm" often conflicts with the necessity of researching the effects of drugs and treatments on pregnant women.*
- Balancing Risks and Benefits: *Researchers must balance the potential risks to the fetus with the necessity to treat the mother effectively. The challenge lies in designing studies that minimally risk fetal health while providing essential data.*

Success Stories and Ongoing Research Efforts

- HIV Treatments and ARTs: *Studies involving antiretroviral therapies (ARTs) for HIV-positive pregnant women have shown significant success.*

- COVID-19 Vaccines: *Pregnant women were included in later-phase clinical trials.*

- Hypertensive Disorders: *Ongoing research into medications for managing hypertensive disorders, such as preeclampsia, during pregnancy.*

Regulations and Guidelines Specific to Pregnant Women

- FDA Regulations: *The FDA has issued guidelines like the "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials" which emphasize the need to include pregnant women in a manner that ensures their protection and the fetus's safety. Reference: FDA Guidance*
- Common Rule (45 CFR 46, Subpart B): *U.S. federal regulations provide additional protections for pregnant women involved in research. It mandates that studies involving pregnant women should offer potential direct benefits to the woman or the fetus, or the risk to the fetus must be minimal.*
- International Ethical Guidelines (CIOMS/WHO): *The International Ethical Guidelines for Biomedical Research Involving Human Subjects addresses the inclusion of pregnant women and instructs that research should be conducted only if it is vital for the population's health.*
- Declaration of Helsinki: *The World Medical Association's Declaration of Helsinki calls for special consideration to be given to vulnerable groups, including pregnant women, emphasizing that research should be based on the needs and priorities of these groups.*

IRB Submission Essentials

- IRB Submission Form: *Complete Supplement VIII, Special Populations, Pregnant Women.*

- Informed Consent Form: *Developing an informed consent form for research involving pregnant women requires careful and comprehensive consideration of the unique ethical and practical needs of this population.*

- Protocol: *When developing a research protocol that includes pregnant women, several special considerations should be addressed to ensure ethical and safe practices.*

- Exempt Research: *Exemption categories apply to research involving pregnant women.*

Pregnant Women – Section Summary

- *Exploring the historical context, reviewing current laws and guidelines, and highlighting successful research initiatives underscores the critical nuances in involving pregnant women in clinical research.*

- *Despite the challenges, adhering to ethical principles and robust regulatory frameworks ensures that both maternal and fetal health needs are met responsibly and inclusively.*

Yale *Human Research Protection Program*

Prisoners in Research

Yale *Human Research Protection Program*

Prisoners in Research

Prisoner: Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing [45 CFR 303(c)].

- In addition, any individual who satisfies the above definition and who is receiving care in a medical treatment setting will be considered a prisoner for purposes of this policy.

Prisoners in Research

- CT statute defines a prisoner as 'any person in the custody of the Commissioner of Correction or confined in any institution or facility of the Department of Correction until released from such custody or control, including any person on parole' (CGS 325 Sec. 18-84).

- The research plan, from recruitment to retention to privacy protections for these individuals, should be carefully designed by the researcher and receive heightened scrutiny from the IRB to ensure that no procedures compromise the safety or status of these participants or otherwise negatively affect their well-being.

Prisoners in Research

- In general, an institution is considered engaged in a particular human subjects research proposal involving prisoners when its employees or agents, for the purposes of the research proposal, obtain:

    1. Data about the prisoner subjects through intervention or interaction with them; or

    2. Identifiable private information about the prisoner subjects.

Prisoners in Research

Historical Unethical Research with Prisoners:

- **Philadelphia's Holmesburg Prison**
  - Prisoners were paid large sums of money to participate in a variety of procedures including radiation procedures with no direct benefit.

Prisoners in Research

OHRP Regulations:

The research under review represents one of the categories of research permissible under **45 CFR 46.306(a)(2);**

(i) The study of the possible causes, effects, and processes of incarceration, and of criminal behavior;

(ii) The study of prisons as institutional structures or of prisoners as incarcerated persons. Research in these two categories is permissible only if the study presents no more than minimal risk, and no more than inconvenience to the subjects (45 CFR 46.306(a)(2));

Prisoners in Research

OHRP Regulations (continued):

The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);

> (iii) research on conditions particularly affecting prisoners as a class; the regulations list as examples vaccine trials and other research on hepatitis, which is much more prevalent in prisons than elsewhere, and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults.
>
> (iv) research on practices, either innovative or accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

Prisoners in Research

OHRP Regulations (continued):

- Waiver for certain epidemiological research
  - The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease.

Considerations for Prisoners in Research

- The institution engaged in the research must certify to the Secretary (through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305; and

- The Secretary (through OHRP) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

Considerations for Prisoners in Research:

- The Bureau of Prisons (BOP) may have additional requirements for research. Each facility may have unique rules and requirements for researchers.
- Access to prisons: Federal, State, Local, County.
- Phases of incarceration
- Juvenile Correctional Facilities

❖Research involving prisoners cannot be "exempt" under the federal regulations.

Considerations for Prisoners in Research:

- Key takeaways:
  - OHRP regulations are there to protect participants.
  - There are different types of correctional facilities, and each has their own governing procedures/policies for research with prisoners.
  - The term "prisoner" extends to individuals who are under the auspices of the department of corrections.
  - Not a population of convenience.
  - **When in doubt always contact the IRB for assistance.**

Yale *Human Research Protection Program*

Decisionally Impaired

Yale *Human Research Protection Program*

Ethical Challenges and Considerations

Informed consent complexities –

- Capacity to Consent: *Individuals who are decisionally impaired may lack the capacity to fully understand the nature, risks, and benefits of the research. This raises concerns about the validity of their consent.*

- Proxy Consent: *Researchers often rely on legally authorized representatives (LARs) or proxy decision-makers to give consent on behalf of the impaired individual, which can be ethically complex.*

Ethical Challenges and Considerations

Assessment of Decision-making Capacity –

- Standardization: *No universally accepted standard exists for assessing decision-making capacity, making it difficult to uniformly apply ethical guidelines.*

- Fluctuating Capacity: *Some conditions may cause capacity to fluctuate over time, complicating the consent process.*

Ethical Challenges and Considerations

Risk-Benefit Analysis –

- Non-therapeutic Research Risks: *When research is non-therapeutic (does not provide direct benefit to the participant), it can be challenging to justify enrolling decisionally impaired individuals.*

- Overprotection vs. Inclusion: *Overprotecting decisionally impaired individuals by excluding them from research can lead to a lack of data on how treatments affect this population, while inclusion needs to ensure their safety and respect.*

Historical Context and Present-Day Challenges

Historical Context for Decisionally Impaired Subjects –

- Early 20th Century: *Lack of Regulations and Ethical Breaches.*

- Development of Ethical Guidelines Specific to Decisionally Impaired:
  - Nuremberg Code (1947): Set of 10 ethical principles for human research.
  - Declaration of Helsinki (1964): Statement of ethical principles for medical research involving human participants.
  - Belmont Report (1979): Identifies the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects.

- Legislation and Current Guidelines Relevant to Decisionally Impaired Subjects:
  - Common Rule (1991) and Subsequent Updates
  - International Guidelines (CIOMS, EU Clinical Trials Directive)
  - The US Health Insurance Portability and Accountability Act (HIPAA) - Privacy Rule

Historical Context and Present-Day Challenges

Recent Ethical Breaches and Lessons Learned for Decisionally Impaired Subjects –

- Historical Ethical Violations: *Guatemalan Syphilis Experiment (1946-1948) represents one of the most notorious examples of unethical research involving vulnerable populations.*

- Contemporary Ethical Breaches: *While significant progress has been made in research ethics, contemporary ethical breaches still occur, including those involving decisionally impaired subjects.*

Success Stories and Ongoing Research Efforts

- Alzheimer's Disease Research: *Clinical trials involving decisionally impaired subjects with Alzheimer's have led to breakthroughs in understanding the disease and developing new treatments.*

- Research on Schizophrenia: *Research involving individuals with schizophrenia, many of whom may be decisionally impaired, has led to the development and refinement of antipsychotic medications.*

- Stroke Rehabilitation: *Research involving stroke survivors, who often experience cognitive impairments, has shown that telehealth interventions can be effective in providing rehabilitation services.*

Historical Context and Present-Day Challenges

Present-Day Challenges for Decisionally Impaired Subjects –

- Complex Consent Processes
- Proxy Decision-Making
- Risk-Benefit Analysis
- Ethical Oversight
- Cultural and Socioeconomic Factors

Regulations and Guidelines Specific to Decisionally Impaired Subjects

Common Rule (45 CFR 46) - US Federal Policy for the Protection of Human Subjects -

- Subpart A: *Baseline protections requiring informed consent and ethical review.*
- Subpart D: *Provides additional protections for children involved as subjects in research, relevant for decisionally impaired minors.*
- Legally Authorized Representatives: *Allows for proxy consent from legally authorized representatives when necessary for decisionally impaired individuals.*

IRB Submission Essentials

- IRB Submission Form: *Complete Supplement VIII, Special Populations, Cognitively Impaired.*

- Informed Consent Form: *Developing an informed consent form for research involving cognitively impaired subjects requires careful and comprehensive consideration of the unique ethical and practical needs of this population.*

- Protocol: *When developing a research protocol that includes cognitively impaired, several special considerations should be addressed to ensure ethical and safe practices.*

Decisionally Impaired – Section Summary

- *The successes and ongoing research efforts highlight the importance of including decisionally impaired individuals in research.*
- *These efforts not only contribute to scientific advancements but also ensure that treatments and interventions are effective and accessible to those who need them most.*
- *By continuing to address the ethical and practical challenges, researchers can build on these successes and foster an inclusive research environment.*

Summary: Populations of Special Interests

- Low socio-economic status
- Illiteracy
- People with disabilities
- People connected to illegal activities
- Students
- Employees
- LGBTQ+

Summary: HRPP Pre-Review & IRB Review Process

Vulnerable Population	Pre-Review	Review
Children	Assent Parental Permission Adult Consent IRB Submission Form PPRC review	Determine the risk level. Permission(s) Required. Compliance with approval criteria. OHRP approval for 407.
Pregnant Women	IRB Submission Form Consent Form and consent Process	Determine the risk level. Consent Requirements. Compliance with approval criteria.
Prisoners	IRB Submission Form Consent Form and consent Process	Determine risk level. Compliance with approval criteria. OHRP concurrence.
Cognitively Impaired	IRB Submission Form Consent/Assent	Determine the risk level. Determine the appropriateness of the plan for consent/reconsent. Compliance with approval criteria.

Additional Resources

- Yale IRB website
- Yale IRES IRB library
- OHRP
- FDA

Questions?

Questions? Contact HRPP@yale.edu
Yale HRPP Website

Yale *Human Research Protection Program*