USE OF HUMAN SUBJECTS IN RESEARCH
PROBLEM: ETHICAL DILEMMA

• Investigators’ dilemma
  • Research designed to provide a major contribution to their field and society in general

VS.

• The rights and welfare of individuals
OBJECTIVES: TO DETERMINE INVESTIGATOR OBLIGATIONS

- History of Human Subjects research, including regulatory background
- Principles of ethical human subject research
- Develop conclusions: Coexistence of ethical human research and successful research, achieving goals
HISTORICAL PERSPECTIVE

• Nazi Medical War Crimes – 1939 to 1945
NUREMBERG CODE – 10 DIRECTIVES:

- **Voluntary consent** of the human subject is absolutely essential
- The experiment must yield **generalizable knowledge** that could not be obtained in any other way and is not random and unnecessary in nature
- Animal experimentation should precede human experimentation
- All **unnecessary physical and mental suffering and injury** should be avoided
- No experiment should be conducted if there is reason to believe that death or disabling injury will occur
- The **degree of risk to subjects** should never exceed the humanitarian importance of the problem
- **Risks** to the subjects should be minimized through proper preparations
- Experiments should only be conducted by **scientifically qualified investigators**
- **Subjects** should always be at liberty to withdraw from experiments
- Investigators must be ready to end the experiment at any stage if there is cause to believe that continuing the experiment is likely to result in injury, disability or death to the subject
HISTORICAL PERSPECTIVE

- The Syphilis Study at Tuskegee
THE SYPHILIS STUDY AT TUSKEGEE

- **Outcomes:**
  - National Research Act of 1974

- 1979 – The Belmont Report
  - Basic Health & Human Subjects Policy for Protection of Human Research Subjects
  - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
THE BELMONT REPORT

• 3 principles essential to conduct of human research
  
  • RESPECT FOR PERSONS
  
  • BENEFICIENCE
  
  • JUSTICE
RESPECT FOR PERSONS

- **Basic principles:**
  - Autonomous agents
  - Additional protection provided for vulnerable participants

- **Challenges:**
  - Human subjects must understand risks & benefits
  - Avoiding coercion or undue influence
BENEFICENCE

- **Basic principles:**
  - Do no harm
  - Maximize benefit & minimize harm

- **Challenge:**
  - How to effectively balance benefit and risk
JUSTICE

• **Basic principles:**
  • Fairness & equity in the distribution of both the burden and the benefits of research participation
  • The single, valid reason for inclusion of a population must be their appropriateness based on the problem being studied

• **Challenge:**
  • Determination of the most appropriate criteria for inclusion/exclusion in a research study that will ensure an equal distribution of harms and benefits
THE HHS REGULATIONS – PROTECTION OF HUMAN SUBJECTS

• The ethical principles for research involving human subjects described in the Belmont Report are codified in the Code of Federal Regulations, 45 CFR 46. The NIH follows all Subparts of the HHS regulations:
  • Subpart A – Basic HHS Policy for Protection of Human Research Subjects
  • Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
  • Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
  • Subpart D – Additional Protections for Children Involved as Subjects in Research
  • Subpart E – Registration of Institutional Review Boards (effective July 14, 2009)
SUBPART A/THE COMMON RULE

The Common Rule

Subpart A
Basic HHS Policy for the Protection of Human Research Subjects
**ADDITIONAL PROTECTIONS**

- **Vulnerable populations**: Specific categories of research are defined in which these populations may participate. There are additional requirements for informed consent and may be other additional requirements.
- **Subpart B** – Pregnant Women, Human Fetuses, & Neonates
- **Subpart C** – Prisoners
- **Subpart D** – Children
- Other “vulnerable” populations include those “…vulnerable to coercion or undue influence”
FEDERALWIDE ASSURANCE

• A FWA is an agreement between Tulane University and DHHS to comply with federal regulations concerning research involving human subjects, including the ethical principles outlined in the Belmont Report and the DHHS regulations 45 CFR Part 46. Tulane University’s FWA registration number is FWA # 2055 from the Office for Human Research Protections (OHRP) in the Department of Health and Human Services.
**INTERNATIONAL RESEARCH**

- 45 CFR 46.101(h) Approval: substitution of alternative policies, codes or regulations to protect human subjects in lieu of the requirements of 45 CFR 46.

- To date, HHS has not deemed any other standards equivalent of 45 CFR 46.
RESPECT FOR PERSONS

USE OF HUMAN SUBJECTS IN RESEARCH
BELMONT REPORT

• “To respect autonomy is to give weight to the autonomous person’s considered opinions and choices while refraining from obstructing his or her actions…”

-Belmont Report
RESPECT FOR PERSONS

- Basic principles:
  - Autonomous agents
  - Additional protection provided for vulnerable participants

- Challenges:
  - Human subjects must understand risks & benefits
  - Avoiding coercion or undue influence
INFORMED CONSENT

- On-going process

- Information exchange continues throughout the research

- Understandable information should include risks and benefits of participation

- Information presented in a “...language understandable to the subject.” (45 CFR 46.116)
WAIVERS OF CONSENT

- Conditions for possible IRB waiver of some/all elements of consent (45 CFR 46.116(d)):
  - No more than **minimal risk**
  - **Not adversely effect rights and welfare** of subject
  - Research could **not be carried out without waiver**
  - When possible, **subjects will receive additional pertinent information** after participation

- **PRACTICABILITY?**
DIMINISHED AUTONOMY

- Factors that can diminish autonomy
  - Age
  - Cognitive impairment
  - Illness
  - Treatments

- Assessments of capacity to consent based on:
  - Level of capacity
  - Complexity & risks involved
LEGALLY AUTHORIZED REPRESENTATIVES (LAR)

• Legally authorized representatives can provide informed consent for individuals with diminished capacity (45 CFR 46.116)
• Obtain informed consent from the participants whenever possible
• If a subject regains the ability to provide informed consent after the research has begun, the subject should be consented before continuing the subject’s participation in the research study
PREGNANT SUBJECTS

- Involving pregnant females in research may affect the woman, the fetus or both. Requirements include:
  - Preclinical studies
  - Risk/benefit analysis must include both the woman and the fetus
- The following are prohibited:
  - Inducements to terminate pregnancy
  - Investigator participation in decisions regarding termination
  - Investigators from determining viability of fetus
VULNERABLE POPULATIONS

- Commonly recognized:
  - Children
  - Pregnant women
  - Prisoners
  - Diminished Autonomy

- Possible Vulnerable Populations: economics, literacy, specific vulnerability to coercion for a variety of reasons

- P.I. must determine whether potential subjects include a “vulnerable population”; if so, make appropriate considerations
CHILDREN IN RESEARCH

• Because children may not have full capacity to consent for research:
  • Children are considered a VULNERABLE POPULATION
  • Children are UNABLE to provide “legally effective informed consent” as required by 45 CFR 46.116
• Children provide ASSENT to participate in research, to the extent that they are capable
• Parents or guardians must provide permission for children to participate in research
ASSENT

• Age, Maturity, Psychological state – all should be considered to determine whether the capacity to provide ASSENT exists in a population
• The LANGUAGE should be age, educationally & developmentally – appropriate
• Waiver options: 46.116
SUMMARY: RESPECT FOR PERSONS

- INFORMED CONSENT: Principle applied through providing voluntary informed consent process
  - Voluntary
  - Subject is capable of appropriate decisions
  - Complete information provided
- Informed consent – required information provided
- Waiver of informed consent
- LAR involvement
- Vulnerable populations
BENEFICENCE

USE OF HUMAN SUBJECTS IN RESEARCH
BELMONT REPORT

• “Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of **beneficence**. The term **beneficence** is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, **beneficence** is understood in a stronger sense, as an **OBLIGATION**.”

-Belmont Report
GENERAL RULES/BENEFIENCE

1. Do No Harm
2. Maximize possible benefits and minimize possible harms
RISK

• Defined: “probability that a certain harm will occur”
• Categories of Risk:
  • Physical
  • Psychological
  • Social
  • Legal
  • Economic
LEVEL OF RISK - DEFINED

- Minimal: “…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” (45 CFR 46.102(i))
PROTECTIONS AGAINST RISK

• PHYSICAL:
  • Adherence to protocols
  • Well-trained research staff
  • Monitoring subjects’ health
  • Recruiting appropriate subjects
  • Referral for clinical care as needed

• PSYCHOLOGICAL:
  • Right to withdraw
  • Counseling referral, if needed
  • Debriefing
PROTECTIONS AGAINST RISK

• SOCIAL:
  • Protecting Confidential Data, including the fact of participation

• LEGAL:
  • Protecting Confidential Data
  • Certificate of Confidentiality, as needed

• ECONOMIC:
  • Protecting Confidential Data
  • May include separation of data from medical records: prevent employers/insurance companies from obtaining information that could put the subject at risk
ANTICIPATED BENEFITS GREATER THAN POTENTIAL HARMs

- **Goal of Research:** Benefit society by contributing to generalizable knowledge about diseases, disorders, public health concerns
- **Participation may:**
  - Benefit Individual participants
  - Neither benefit nor harm individual participants
  - Pose risks to individual participants
- **Regulations regarding participants require:**
  - Risks are minimized
  - Unavoidable risks are justified
  - Studies progress toward important, generalizable knowledge
REGULATORY REQUIREMENTS

After minimizing risks to the greatest extent possible, investigators must provide:
1. Protections against risk
2. Potential benefits to subjects
3. Importance of the knowledge to be gained
COMPENSATION FOR PARTICIPATION

- Compensation is FAIR and APPROPRIATE

- Information must be provided to the subjects regarding:
  - Availability
  - Requirements for receiving full, partial or no compensation
  - Information: Compensation as reimbursement
UNDUE INDUCEMENTS

- Inducements unduly influential; inappropriate
- The level/kind of compensation considers subjects’ vulnerabilities
- Possibly impairs subjects’ perception of risks or subjects’ judgment
- May prompt subjects to lie/conceal information that may disqualify
AVOID THERAPEUTIC MISCONCEPTION

• Protocols may include examinations, diagnostic tests, interactions with healthcare providers plus experimental interventions

• Subject may believe in a guaranteed health benefit

• Subjects ignore risks related to participation due to expectation: participation designed for individual benefit.
PRINCIPLE OF BENEFICENCE

- Investigators must consider all factors, including:
  - Equipoise
  - Protecting privacy of participants and confidentiality of data
  - Establishing oversight to protect the rights and welfare of participants and determine the significance of data
INSTITUTIONAL REVIEW BOARDS (IRB)

• Specialized committees required by regulations that safeguard the rights and welfare of human subjects.

• Determine “...the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice” (45 CFR 46.107)
IRB – MAJOR ROLES

- Initial review
- Informed consent
  45 CFR 46.116
- Continuing oversight
- IRB membership
  45 CFR 46.107 requires: 5 members from a variety of backgrounds

- If appropriate expertise is lacking, people with appropriate expertise invited to assist
GENERAL CRITERIA FOR IRB APPROVAL

- Risks minimized
- Risks are reasonable related to benefits/importance of knowledge
- Selection of subjects is equitable
- Informed consent sought, based on 45 CFR 46.116

- Informed consent appropriately documented, 45 CFR 46.117
- Adequate provision for monitoring data to ensure subjects safety; adequate provisions to protect privacy/maintain confidentiality of data
EXPEDITED REVIEW

• Alternative review method: “certain types” of research
• No more than “minimal risk”/minor changes to existing research
• Expedited review conducted by the IRB chair or designated experienced IRB member (45 CFR 46.110)
• Expedited review conducted by fewer individuals; follows same regulations, equally stringent, not necessarily faster
• Expedited submissions may be determined by a reviewer to require Full Board Review
DATA AND SAFETY MONITORING PLAN

- DSM P describes protections: subjects, data integrity and oversight
- Plan = risks of participating in the research; method/frequency of monitoring directly related to the possible harms
- 45 CFR 46.11: studies involving human subjects should have a monitoring plan
- NIH requires that all clinical trials have a plan
DATA AND SAFETY MONITORING BOARDS

- **Range of Monitoring**: Oversight by PI and IRB for a single-site, minimal risk clinical trial, to Oversight by full Data and Safety Monitoring Board (DSMB) and IRB(s) for a multi-site trial that involves greater than minimal risk.

- **DSMBs** are committees of experts who have no bias with respect to the research and may be permitted to periodically view unblinded data and conduct interim analyses. PIs must not view unblinded data while the study is ongoing.
SUMMARY: BENEFICENCE

- Beneficence principle involves maximizing benefits and minimizing harms to research participants
- Subjects reviewed include:
  - Protections against risk
  - Definition of minimal risk
  - Risk benefit analysis
  - Potential benefits for subjects
  - Compensation for subjects
  - Equipoise
  - Privacy and Confidentiality
  - Coded information to protect confidentiality
  - IRB oversight & expedited review
  - Data and Safety Monitoring
“Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.”

- Belmont Report
DEFINITION OF JUSTICE

1. Fair procedures and outcomes are used to select research participants
2. There is a fair distribution of benefits and burdens to populations who participate in research
TWO KINDS OF JUSTICE

The Belmont Report defines two types of justice:

- **Social Justice**: “...requires that distinction be drawn between classes of subjects that ought and ought not to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons.”

- **Individual Justice**: “…should not offer potentially beneficial research only to some patients who are in their favor or select only ‘undesirable’ persons for risky research.”
EQUITY VS. EQUALITY

• Defined:
  • Equitable treatment – treated FAIRLY
  • Equal treatment – treated exactly the SAME WAY

• Research should strive for equitable distribution of risks and benefits. Investigators treat subjects FAIRLY and JUSTLY. It does not mean that all subjects are EQUALLY REPRESENTED but that their representation is fair and just, based on the risks and benefits associated with the research
EQUITABLE DISTRIBUTION

• Requires investigators to determine the distribution of different groups in the populations that:
  • May be affected by the disease or condition being researched
  • Are anticipated to benefit from the knowledge gained through the research

• Ensure that subjects recruited are not unduly burdened; recruitment must reflect the diversity of the population involved
NIH INCLUSIONS: WOMEN & MINORITIES

• The Justice Principle is applied through the inclusion of women and minorities in human subjects research.

• Investigators must determine whether the intervention or therapy in the research affects women, men or members of minority groups and subpopulations.
INCLUSION OF CHILDREN

• The Principle of JUSTICE applies to the inclusion of children in research
• Basis: Children receive treatments only tested in adults; there is insufficient data on safe and effective uses for many treatments used for children
• Result of “protecting” children from research:
  • Children have been denied the benefits of participation in research
  • Prevention of gathering adequate data about the effects of many treatments in children
INCLUSION OF CHILDREN

• NIH position: children must be included in all NIH-supported human subjects research unless “…there are scientific and ethical reasons not to include them”

• Policy exceptions are published
REGULATIONS DEFINING “CHILDREN”

• HHS: (45 CFR 46.402) “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”

• NIH: “Individuals under the age of 21”
JUSTICE IN USE OF PLACEBOS

- Therapeutic Misconception – Subjects ignore risks posed to their own well-being by participation in research due to a belief that every aspect of their participation has been designed for their own benefit
- Deception – Misleading subjects about the research purpose or procedures
- Justifications:
  - No approved, effective treatment exists
  - No agreement regarding appropriate treatment
  - Placebo risk is minimal risk
  - If widespread/major benefits are expected to result & placebo risk is minimal risk
DEBRIEFING

- When deception occurs, debriefing after the end of the study generally occurs.
- May depend on whether disclosure may result in harm.
- If the debriefing will benefit the subject by correcting misperceptions or reducing pain, stress or anxiety, then it is appropriate.
JUSTICE IN INTERNATIONAL RESEARCH

• Questions regarding fair treatment & fair standards
  • Scare resources
  • Pronounced vulnerabilities

• Ethical questions:
  • Conducting in poor settings without exploitation
  • Debt to host country following research
  • Standards & assurances used to protect subjects
  • Negotiation of regional or cultural differences
  • Cultural values that impact informed consent
  • Sustaining benefits to subjects after study completion
SUMMARY: JUSTICE

- Requirements:
  - Fair procedures & outcomes in the selection of research subjects
  - Equal distribution of benefits and burdens of research
  - Benefits of participation shared across diverse, eligible populations
  - Risks of participation are equally shared by the diverse populations
  - The ability of members of the class to bear burdens
  - Appropriateness of placing additional burdens on an already over-burdened class
QUESTIONS?

USE OF HUMAN SUBJECTS IN RESEARCH
THANK YOU

USE OF HUMAN SUBJECTS IN RESEARCH
RESOURCES

- https://humansubjects.nih.gov/
- http://ori.hhs.gov/education/products/montana_round1/human.html
- https://www.citiprogram.org/index.cfm?pageID=88
- http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRHome.htm
RESOURCES

- https://docs.gatesfoundation.org/Documents/Human_Subjects.pdf
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3601707/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547525/
RESOURCES

- http://jme.bmj.com/content/31/1/35.full
- http://www.ahrq.gov/funding/process/grant-app-basics/hsubjects.html
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082641/
- http://ccnmtl.columbia.edu/projects/cire/pac/foundation/#1_1