ETHICS OF HUMAN SUBJECTS RESEARCH

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MILDRED CHO

OVERVIEW

- What is human subjects research?
- How is human subjects research regulated?
- Why is human subjects research regulated?
- What do regulations have to do with the ethics of human subjects research?
- Strategies for thinking about ethical issues
- Research scenarios - discussion

WHAT IS HUMAN SUBJECTS RESEARCH?

- The Common Rule 45 CFR 46 has been significantly revised
- Revisions (new Final Rule) take effect January 21, 2019
- Include changes to definition of human subjects research, exemptions, secondary research with identifiable information and biospecimens, informed consent

https://about.citiprogram.org/en/final-rule-resources/#newrevised

WHAT IS A HUMAN SUBJECT?

- Current Common Rule
- (f) *Human subject* means a **living individual** about whom an investigator (whether professional or student) conducting research obtains

  (1) **Data** through **intervention** or **interaction** with the individual, or
  (2) **Identifiable private** information.

- Revised Common Rule
- Human subject means a **living individual** about whom an investigator (whether professional or student) conducting research:

  (i) Obtains information or biospecimens through intervention or interaction with the individual, **and uses, studies, or analyzes** the **information or biospecimens**; or

  (ii) Obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**.

WHAT IS RESEARCH?

- 45 CFR 46.102 – definition unchanged
  - (d) *Research* means a **systematic investigation**, including research development, testing and evaluation, designed to develop or contribute to **generalizable knowledge**. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

WHAT IS **NOT** HUMAN SUBJECTS RESEARCH?

- oral history, biography, historical scholarship
- journalism, literary criticism, legal research
- public health surveillance
- criminal justice or criminal investigative activities
- activities in support of intelligence, homeland security, defense, or other national security missions

HOW IS HUMAN SUBJECTS RESEARCH REGULATED?

- Non-binding international guidelines:
  - WMA Declaration of Helsinki, UN Council for International Organizations of Medical Sciences (CIOMS)
- US regulations other than the Common Rule:
  - FDA
  - CDC, USDA, EPA

OTHER MAJOR CHANGES TO THE COMMON RULE

- Exemptions
  - http://research-compliance.umich.edu/human-subjects/common-rule-other-changes/u-m-implementation-exemption-changes
- Secondary research with identifiable information and biospecimens
- Informed consent
  - http://research-compliance.umich.edu/human-subjects/common-rule-other-changes/u-m-implementation-informed-consent-changes

#1 - EDUCATIONAL EXEMPTION

- **What's New:** A new *ineligibility* criterion will be added to this interaction/intervention exemption for research that involves possible "adverse effects" on student learning of the required education content and/or on the assessment of educators.

#2 - SURVEYS, INTERVIEWS, EDUCATIONAL TESTS, AND OBSERVATION OF PUBLIC BEHAVIOR

- **What's New:** The scope will be expanded to include the collection of sensitive and identifiable data. However, the following is not allowed:
  - Interventions
  - The collection of biospecimens
  - Linking to additional personally-identifiable data
  - Research with children (*except* for educational tests or some public observation)

3 - BENIGN BEHAVIORAL INTERVENTION (NEW)

- **What's New:** This new exemption permits data collection via an interaction (e.g., survey, interview, audio/visual recording) from adult subjects with prospective agreement. However, the following is **not allowed**:
  - Research with children
  - Deception, unless prior agreement obtained
  - Physiological data collection methods (e.g., EEG; wearable devices, such as FitBit™; blood pressure monitors)
  - Linking to additional personally-identifiable data

#4 - SECONDARY RESEARCH (IDENTIFIABLE PRIVATE INFORMATION/BIOSPECIMENS)

- **What's New:** The scope of this exemption will be expanded to allow:
  - Prospective data review
  - Maintenance of identifiers, if **all** study data is protected health information (PHI)
  - Research that is conducted by, or on behalf of, a Federal department/agency or using government-generated or government-collected information obtained for non-research activities

#5 - PUBLIC BENEFIT/SERVICE PROGRAM RESEARCH (FEDERAL DEMONSTRATION PROJECTS)

- **What's New:** A new *eligibility* criterion for this interaction/intervention exemption will be that the project must be published on a federal website.

#7 - STORAGE / MAINTENANCE OF IDENTIFIABLE DATA/BIOSPECIMENS OBTAINED WITH "BROAD CONSENT" (NEW)

- **What's New:** This new exemption allows for the storage of data and/or specimens in a repository, with identifiers maintained, that were collected under an approved IRB protocol with "Broad Consent" for future secondary use research.

#8 - USE OF IDENTIFIABLE DATA/BIOSPECIMENS OBTAINED WITH "BROAD CONSENT" (NEW)

- **What's New:** This new exemption allows for secondary research use/analysis of identifiable data/biospecimens that were collected under an approved IRB protocol with "Broad Consent".

https://about.citiprogram.org/en/final-rule-resources/

Final Rule Material:
Secondary Research with Identifiable Information and Biospecimens

How can secondary research with identifiable private information or identifiable biospecimens be conducted under the Final Rule?

Action	Explanation
Make the Information or Biospecimens Non-Identifiable	No substantive change from pre-2018 rule; secondary use of non-identifiable information or biospecimens is still exempt.
Obtain IRB Approval for Research with an IRB Waiver of Consent	Same practice as currently exists under pre-2018 rule with waiver; however, there are some new limits on when IRBs can waive consent.
Obtain IRB Approval for Research with Prospective Consent from Subjects	Only change from pre-2018 rule is that the Final Rule requires informed consent forms to include new required language about secondary use of information or biospecimens.
NEW Use the Broad Consent Option	New option for secondary research use of identifiable information or biospecimens.
UPDATED Make Use of Expanded Exemption 4 Criteria	Updated options to use exempt category 4. For instance, secondary research projects where the identifiable information is protected under Health Insurance Portability and Accountability Act (HIPAA) requirements now may qualify as exempt from the Final Rule.

BROAD CONSENT

- Under the current regulations, secondary research use of identifiable data/biospecimens is permissible through study-specific consent, by obtaining an IRB waiver of consent, or by removal of identifiers.
- In the revised Common Rule, "Broad Consent" is an (optional) alternative consent process for use **only** for the storage, maintenance, and secondary use of identifiable private information or **identifiable biospecimens** for future, yet-to-be-specified research. To utilize "Broad Consent," the study team and/or the unit/biorepository responsible for the storage of the identifiable data/biospecimens are required to:
  - identify the types of research that may be conducted with the data/biospecimens,
  - **record and track who has agreed to or refused** consent, and
  - to **track the terms of consent** to determine whether proposed future secondary research use falls within the scope of the identified types of research

When your project will involve...	Include in the informed consent...
The collection of identifiable private information or identifiable biospecimens	A statement indicating whether: •identifiers may be removed, and •**de-identified** information or biospecimens **may or may not be** used or shared for future research
Use of biospecimens	A statement indicating whether: •biospecimens may be used for commercial profit, and •the subject will share in that profit
Clinically relevant results	A statement indicating whether the clinical results, including individual research results, will be returned to the subject, and if so, under what conditions
Whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen	A statement indicating that the research will or might include whole genome sequencing

WHY IS HUMAN SUBJECTS RESEARCH REGULATED?

- Rewriting of the social contract with professionals

WHY IS HUMAN SUBJECTS RESEARCH REGULATED?

- People unwillingly or unwittingly subjected to medical experiments that posed significant risks and offered no benefit to them individually
  - Nazi experiments, Tuskegee, Willowbrook
  - Operation Whitecoat, Project MKUltra

WHY IS HUMAN SUBJECTS RESEARCH REGULATED?

- Even recent research has led to changes in oversight

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SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

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BOSTON

BEECHER –3 EXAMPLES OF 50

- Penicillin withheld from 109 servicemen with streptococcal respiratory infections
- “Challenge” doses of drug administered to 50 healthy patients, including children who were “mental defectives” and “inmates of a children’s detention center” with liver biopsies to determine hepatic dysfunction
- Deliberate induction of hypotension (av. 53mm Hg) and bradycardia (42/20) in 50 surgical patients by manipulation of peritoneum, gallbladder, portal and caval veins.

November 15, 1958

Willowbrook Study
Staten Island, New York

Dear Mrs. _____:

We are studying the possibility of preventing epidemics of hepatitis on a new principle. Virus is introduced and gamma globulin given later to some, so that either no attack or only a mild attack of hepatitis is expected to follow. This may give the children immunity against this disease for life. We should like to give your child this new form of prevention with the hope that it will afford protection.

Permission form is enclosed for your consideration. If you wish to have your children given the benefit of this new preventive, will you so signify by signing the form.

BEECHER - CONCLUSIONS

- "…it is absolutely essential to strive for [informed consent] for moral, sociologic and legal reasons…"
- "The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and unless all hazards are made clear."
- "…there is the **more reliable safeguard** provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."
- "The gain anticipated from an experiment must be commensurate with the risk involved."
- "An experiment is ethical or not at its inception; it does not become ethical *post hoc* – **ends do not justify means**."

WHAT DOES THIS HAVE TO DO WITH ETHICS?

- Ethics (the answer to the question “What should I do?”) are best understood in the framework of one or more relationships and the associated responsibilities, obligations or duties
  - E.g., general, scientific, clinical, professional responsibilities
  - Responsibilities arise from a social contract – some elements may be embedded in law and regulation
  - There are multiple stakeholders in any action, whose interests must be balanced

WHAT MAKES CLINICAL RESEARCH ETHICAL?

- Emanuel, Wendler & Grady *JAMA* (2000) 283:2701
- Important because the scope of IRB review is limited by regulation
  - 45 CFR 46.111: “The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.”

WHAT MAKES CLINICAL RESEARCH ETHICAL?
(EMANUEL, 2000 JAMA)

Social/scientific value
Scientific validity
Fair subject selection
Favorable risk/benefit
Independent review
Informed consent
Respect for potential and enrolled subjects

Requirement	Justifying value or principle
Informed consent Providing adequate and appropriate information Voluntary decision-making	Respect for subject autonomy
Respect for potential and enrolled subjects Permitting withdrawal Protecting privacy Providing new information about risks and benefits Providing results Maintaining welfare	Respect for autonomy and welfare

Requirement	Justifying value or principle
Favorable risk-benefit ratio Minimize risks to subjects Enhance potential benefits to subjects Potential benefits to subjects and society outweigh risks	Non-maleficence, beneficence, nonexploitation Can't make risks acceptable by offering extraneous benefits "Risk-knowledge calculus" for early phase research
Fair subject selection Inclusion not based on convenience or privilege Inclusion and exclusion based on scientific validity or minimizing risks	Justice Those who bear risks and burdens must be in a position to enjoy benefits Risks and benefits distributed fairly

Requirement	Justifying value or principle
Scientific or social value To health, knowledge Implementable	Scarce resources, nonexploitation Addressing priorities Avoiding unnecessary harm
Scientific validity Valid, reliable methods Minimize bias “Honest” null hypothesis	Scarce resources, nonexploitation Maximizing benefits Justifying exposure to risks
Independent review	Public accountability

STRATEGIES FOR THINKING ABOUT ETHICAL ISSUES

- Some (Western) ethical approaches
- Consequentialism – e.g. Willowbrook study of hepatitis
- Utilitarianism – what is the greatest amount of good for the greatest number? Or what is the best possible balance of good over evil?
  - The sum of individual utilities is a measure of social welfare
  - E.g., Elon Musk re: Tesla Autopilot: “If you’re writing an article that’s negative that essentially dissuades people from using [autonomous tech],” he told reporters, “you're killing people.”

STRATEGIES FOR THINKING ABOUT ETHICAL ISSUES

- Deontology – What is my duty? What are my rights? What are the applicable rules or principles and how are they applied?
  - E.g., duty of confidentiality/ right to privacy
- Based on social roles, agents
  - E.g., non-maleficence for a doctor towards a patient vs. non-maleficence of a public health official
  - E.g., parental, doctor's and researchers' roles in developing and using genetic modification to alter traits in children

STRATEGIES FOR THINKING ABOUT ETHICAL ISSUES

- Context matters: Who, what, when, where, why
  - Good Samaritan vs. duty of rescue, duty to warn
  - Scalpels in the OR vs. assault and battery
  - Research involving genetic editing of human embryos: science vs. creating genetically modified humans
- Quality of argument matters

SCENARIO 1

- You are testing effects of a high resolution video camera feed of outdoor public spaces into windowless offices on psychiatric health and productivity of office workers. You are able to mount the cameras on campus and display the video feeds on large HD screens into offices of co-workers who do not have windows.

SCENARIO 2

- You are conducting a study of implants to improve visual acuity in healthy volunteers, and part of routine data collection involves measurement of blood pressure. You will collect data from participants every month for 6 months. At the first of their monthly visits, one participant has an extremely high systolic blood pressure of 200 mm Hg. To follow up on this finding, you tried to reach him by phone, email and by letter via the contact information he gave upon enrollment, but did not get any reply after a month. He does not show up for his second monthly visit.

SCENARIO 3 PART 1

- Through mouse studies, you identified genetic variants that protect against DNA damage by ionizing radiation, and that encode regulators of DNA repair enzymes. You also found that, in mice, these variants are also associated with increased frequency of incidence of autoimmune disorders triggered by exposure to specific common viruses. However, because of their potential to identify people who might be better suited to long-term space flight, you want to determine frequencies of these alleles in human populations and examine whether they appear to provide similar protection against radiation-induced DNA damage in humans.

SCENARIO 3 PART 2

- You are able to get access to tissue samples from pilots who work at a commercial air freight company who conduct long-haul flights. The samples have been collected longitudinally over several years and are linked to the pilots' identities through a code that you can access. You find variants of the human homologs of the mouse genes in several blood samples, which also appear to be associated with reduced DNA damage.

SCENARIO 3 PART 3

- You are also interested in studying factors associated with flight performance and sleep deprivation, and in addition to tissue samples from pilots, you have access to real-time data streams collected in the cockpit and from the pilots' use of mobile devices in the air and between flights. These include keystroke dynamics and voice patterns. Keystroke speed and certain types of voice patterns have been associated with depression as well as being a potential very early indicator of Parkinson's disease.