Ethical issues in human experimentation

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Overview

• Unethical studies
• Historical motivation
• Principles governing research
• Background to institutional review boards
• Case studies

The Immortal Life of Henrietta Lacks by Rebecca Skloot

• Her name was Henrietta Lacks, but scientists know her as HeLa. She was a poor Southern tobacco farmer who worked the same land as her slave ancestors, yet her cells—taken without her knowledge—became one of the most important tools in medicine. The first "immortal" human cells grown in culture, they are still alive today, though she has been dead for more than sixty years. If you could pile all HeLa cells ever grown onto a scale, they’d weigh more than 50 million metric tons—as much as a hundred Empire State Buildings. HeLa cells were vital for developing the polio vaccine; uncovered secrets of cancer, viruses, and the effects of the atom bomb; helped lead to important advances like in vitro fertilization, cloning, and gene mapping; and have been bought and sold by the billions.

Tuskegee Syphilis Study

• US Public Health service ran a study from 1932 to 1972 on syphilis
• 399 poor Black share croppers were told they were being treated for "bad blood," but in fact had syphilis and were untreated for syphilis
• Local physicians were given subject lists of people not to treat
• Initially no syphilis treatment was available, but by 1947 penicillin, the standard treatment, was withheld from these men
  – Men died
  – Families infected
• For participating in the study, the men were given free medical exams, free meals and free burial insurance
• Stopped in 1972 after PHS employees leaked info to the press
• "I don’t know what they used us for. I ain’t never understood the study." – a survivor
• Info at http://www.cdc.gov/nchstp/od/tuskegee/
• (wary of medical profession)
Jewish chronic disease hospital case

- Not the 'monster'
- 1963
- Cancer patients reject foreign cancer cells more slowly
  -  
- So took immunosuppressed patients and injected saline or foreign cancer cells; won’t get cancer just see how long to take rejection
- Decided not to burden patients with details
- Hearing

Willowbrook State school, NY

- 1956-1971
- New wing of institution: injected with sanitized extract of fecal matter (some get controls)
- Good science
- Using children as guinea pigs, feeding them hepatitis

Nuremberg

During the Nuremberg War Crimes Trials, 23 German doctors were charged with crimes against humanity for...

- ...performing medical experiments upon concentration camp inmates and other living subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts...

Hypothermia experiments

The Nazis immersed their subjects into vats of ice water at sub-zero temperatures, or left them out to freeze in the winter cold. As the prisoners excreted mucus, fainted and slipped into unconsciousness, the Nazis meticulously recorded the changes in their body temperature, heart rate, muscle response, and urine.
Cannot trust physicians

• All at same time
• Greater safeguard and protection
• National Commission for protection of human subjects and behavioral research
• Set of principles to regulate and govern research
• Diverse individuals

Bioethics

• Awesome advance of biomedical research
  – Both experimental/basic
  – And clinical

• Originally problems more in medical ethics
  – Abortion
  – Euthanasia
  – Reproductive technologies

Neuroethics

• Ethical issues in enhancement
  – Gingko biloba, prozac (SSRI), ritalin

• Court-ordered CNS intervention
  – Aggressive behavior -> SSRI, fluoxetine
  – Sex offenders subject to pharmacological treatment

• Mind reading
  – Can classify some by scans (introversion vs extroversion); advertising agencies now interested too
  – Drug-free addicts show strong PET activation in amygdala, anterior cingulate and orbitofrontal cortex to paraphernalia

Other issues for discussion

• Intellectual property: who owns the ideas?
  – models of research–individual researcher versus research teams? Advisor versus student?

• Authorship issues (discipline independent ideas)?

• Research applications
  • Relationship to source of funding?
Other longstanding issues

- How safe are new methods
  - High res fMRI, TMS
- What is the course of action when an abnormality is detected on imaging?
- How much should one divulge to a subject?
- What considerations guide new therapies for diseases such as Parkinson's?
  - Fetal transplant?
- Genetic testing for Huntington's disease?
- Ethics of psychosurgery?

Basic principles

- RESEARCH is defined as a "systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge"
- HUMAN SUBJECT is defined as 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"

Human experimentation

- Set of scientific activities the primary purpose of which is to develop or contribute to generalizable knowledge about the chemical, physiological or psychological processes involved in human functioning
- Called 'human experimentation’ because uses humans as subjects
- Therapeutic research versus nontherapeutic research

Basic principles

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National Research Act

- 1974 National Research Act (Pub. L. 93-348)
  - Established the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research"
  - Identify basic ethical principles
  - Develop guidelines to assure research is carried out according to those principles
  - Required IRBs at institutions receiving HEW (HHS) support for human subjects research
  - February 1976 - Held four-day conference at Smithsonian Institution’s Belmont Conference Center

Belmont Report

- Led to Belmont report (1979)
  Ethical Principles and Guidelines for the Protection of Human Subjects of Research
  - [http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm](http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm)

Principles of Research with Human Subjects

- Respect for Persons
  - individuals have autonomy and choice
  - people can not be used as a means to an end
  - provide protection to the vulnerable
  - provide informed consent and privacy
- Beneficence
- Justice

Principles of Research with Human Subjects

- Respect for Persons
- Beneficence
  - kindness beyond duty
  - obligation to do no harm
  - obligation to prevent harm
  - obligation to do good
  - minimize risks, maximize benefits
- Justice
Principles of Research with Human Subjects

- Respect for Persons
- Beneficence
- Justice
  - treat all fairly
  - share equitably burdens and benefits

Federal Regulation

- Belmont principles instantiated in “common rule”
- System of Institutional Review Boards (IRBs) to monitor human subject research
- Federal regulations for treatment of human subjects
  - http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

Principles from Belmont Report

- Basic Ethical Principles
  1. Respect for Persons
  2. Beneficence
  3. Justice

- Applications
  1. Informed Consent
  2. Assessment of Risk and Benefits
  3. Fair selection of Subjects

Instantiated in “common rule”

- System of Institutional Review Boards (IRBs) to monitor human subject research
- Federal regulations for treatment of human subjects
  - http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

Self-Interest: High Profile Shutdowns

- April 1998 Office of Protection from Research Risks (OPRR) cites the University of Maryland at Baltimore for certain systemic weaknesses in its protections for human research participants. The University was cited for inadequate oversight of research involving human subjects and failed to ensure that informed consent was obtained.

- October 1998 OPRR issues a letter of noncompliance to the University of California, San Francisco, for failing to adequately protect human subjects in research. The university was cited for not ensuring that research involving human subjects was conducted in accordance with federal regulations.

- May 1999 OPRR suspends research at Duke University due to administrative deficiencies in the Institutional Review Board (IRB) process. The university was cited for failure to ensure that informed consent was obtained from all subjects.

- August 1999 The Chancellor of the University of Illinois at Chicago resigns after an OPRR suspends research. Violations include failure to obtain proper informed consent from all subjects in research projects and failure to obtain IRB approval before beginning research.

- September 1999 OPRR suspends research at the University of Pennsylvania due to violations of federal regulations. The university was cited for failure to ensure that research involving human subjects was conducted in accordance with federal regulations.

- January 2000 OPRR suspends research at Virginia Commonwealth University for not providing adequate information to research volunteers. The university was cited for failure to ensure that research involving human subjects was conducted in accordance with federal regulations.

- January 2000 OPRR suspends research at the University of Alabama at Birmingham for failing to ensure that research involving human subjects was conducted in accordance with federal regulations. The university was cited for failure to ensure that informed consent was obtained from all subjects.

- July 2000 OPRR suspends research at the University of Texas due to violations of federal regulations. The university was cited for failure to ensure that research involving human subjects was conducted in accordance with federal regulations.

- September 2000 OPRR suspends research at the University of Miami for failing to ensure that research involving human subjects was conducted in accordance with federal regulations. The university was cited for failure to ensure that informed consent was obtained from all subjects.

- September 2000 OPRR suspends research at the University of Oklahoma for failing to ensure that research involving human subjects was conducted in accordance with federal regulations. The university was cited for failure to ensure that informed consent was obtained from all subjects.

- September 2000 OPRR suspends research at the University of Florida and Yale University for failing to ensure that research involving human subjects was conducted in accordance with federal regulations. The university was cited for failure to ensure that informed consent was obtained from all subjects.

- June 2001 OPRR suspends research at Johns Hopkins due to violations of federal regulations. The university was cited for failure to ensure that research involving human subjects was conducted in accordance with federal regulations.

- September 2000 OPRR suspends research at the University of Texas and University of Miami, respectively, for failing to ensure that research involving human subjects was conducted in accordance with federal regulations. The university was cited for failure to ensure that informed consent was obtained from all subjects.

- September 2000 OPRR suspends research at the University of Florida for failing to ensure that research involving human subjects was conducted in accordance with federal regulations. The university was cited for failure to ensure that informed consent was obtained from all subjects.

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Training To Do Human Subjects Research

- All human subjects research at CMU must be reviewed by the IRB
  - [http://www.cmu.edu/provost/spon-res/compliance/hl.htm](http://www.cmu.edu/provost/spon-res/compliance/hl.htm)
- Researchers have a responsibility to know how to conduct research ethically
- Federal government requires training for ethics in research
  - You need to complete training
  - Many have an explicit health/medical focus

Risk Should Be Proportional to Benefit

- Risk to human subjects need to be justified by benefit
  - Most behavior research involves minimal risk
  - Research procedures have "minimal risk" if the risks associated with the research procedures are no more that experienced by participant in non-research setting
    - Probability of harm X magnitude
- Even highly risky research can be justified if the potential benefits are great enough
- Even minimal risk research isn’t justified if no one benefits
  - E.g., Because of poor research design

Spectrum of Risk

- Physical or psychological harm during procedures
- Revealing private, privileged or embarrassing information, which puts participants at risk
  - Maintain confidentiality of data
    - Separate data from identifiers
    - Keep data in secure location and available only to research staff
      - Poor computer security is a major problem
    - Obtain special consent when collecting video, since subject is recognizable

Minimize Harm
Confidentiality of Data

- Researcher has the responsibility to keep confidential any identifiable information that puts participants at risk of criminal or civil liability or is damaging to the subjects' financial standing, employability, or reputation.
- Degree of concern over confidentiality depends on sensitivity of the information:
  - E.g., Public opinion survey on pop culture vs. survey on criminal behavior that asks about crimes committed and drug use.
- For high risk information, apply for Certificate of Confidentiality from NIH, which precludes government subpoena of data for civil or criminal cases.

Informed consent

- Research participation must be completely voluntary.
- Participants need all relevant information to help them make an informed decision about participation:
  - Risks & benefits
  - Opportunity to withdraw.
- Inform participants in easy-to-understand language.
- Don’t use your power to coerce cooperation:
  - E.g., teaching position
  - E.g., employee status.
- Get informed consent from guardians of those who can’t give informed consent:
  - Minors “assent”.
- Behavior in “public place” is ambiguous in the Internet era.

Four Types of Research

- Excluded: Either not research or no human subjects involved.
- Exempt: Human-subjects, but exempt for federal regulations:
  - IRB needs to give you the exemption.
- Expedited review:
  - Minimal risk.
  - Reviewed by one IRB member, first-come-first serve.
- Full board review:
  - Not minimal risk.
  - Reviewed at monthly meeting by full board.

Decision Tree for IRB Review

- Q.1. Is the proposed activity research? Yes → Q.2. Does the research activity involve human subjects? Yes → A: PI thinks research is exempt. No → Proceed with your research.
- Q.2. Does the research activity involve human subjects? Yes → A: Research is not exempt. No → PI fill out exempt Form. Proceed with your research.
- Q.3. Is the research exempt from IRB review & approval? Yes → PI fill out HS protocol. Proceed with your research. No → IRB determines if it is exempt & notifies PI. Proceed with your research.

When Approved, proceed with your Research.
Excluded Activities

- If it’s not research.
  - Research = systematic data collection designed to develop or contribute to generalizable knowledge.
  - Many design and engineering exercises are not research by this standard.
- If it doesn’t involve human subjects
  - Living person about whom an investigator obtains
    - Data through intervention or interaction or
    - Identifiable private information

Exempt Research

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices.
- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
  - (i) human subjects are selected on the basis of a characteristic or behavior (including, without limitation, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
- (3) If not exempt by (2)
  - (i) if the human subjects are elected or appointed public officials or candidates for public office:
  - or (ii) Federal statute(s) require(s)
    - (a) procedures for obtaining benefits or services under those programs;
    - (b) procedures for obtaining benefits or services under those programs.
- (4) Research involving the collection of existing data, documents, records, or specimens.
- (5) Research and demonstration projects, designed to — examine:
  - (i) Public benefit — programs
  - (ii) procedures for obtaining benefits or services
    - from those programs.
- (6) [Food Evaluations]

IRB determines whether research is exempt
Case study

• A college senior is conducting a senior thesis. She wants to conduct an online survey online of participants in a pro-anorexia movement. Minors are not allowed to consent to research, and need parental permission. She estimates that up to half of her subject population are minors. She is willing to exclude minors from her sample, but is having trouble convincing her Institutional Review Board that she is able to exclude minors. She has placed the age requirement prominently in the informed consent form, and will also have participants email me (at an address created for this study) a statement declaring their ages.

Case study

• A researcher in computer science needs a corpus of mail messages to develop machine learning techniques to identify action requests in messages. He locates five faculty members, who agree to give him relevant archives all the messages they exchanged when they were organizing conferences. Does he need to get permission from the senders of the messages? Does he need to get permission of people mentioned in the messages?

Reasonable expectations of privacy

• Fussell: Does peer support in a mental health group improve mental health, as revealed by conversational analysis
• What about if group had this in welcome screen
  • "NOTICE FOR JOURNALISTS AND RESEARCHERS: The users of this site request that you ask for permission from all direct participants before quoting any material collected here." (telnet://lambda.moo.mud.org)

Get advice

• You are a self-interested party. Get unbiased advice before proceeding
• At CMU, all research involving human participants requires IRB approval
  – Most get expedited reviews, with a “minimal risk” determination
  – Office of the Provost
  – Components
    • Draft proposal, description of how subjects are treated, sample consent form, confidentiality procedures, risk/benefit analysis
Informed Consent Checklist

- A statement that the study involves research
- An explanation of the purposes of the research
- A description of the procedures to be followed
- Identification of any procedures which are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any reasonably foreseeable benefits to the subject or to others which may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs or, if so, what they consist of, or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled

Sample Informed Consent Form

- http://www.irb.umn.edu/consent/templateconsent.rtf

- CONSENT FORM

- You are invited to be in a research study of [insert general statement about study]. You were selected as a possible participant because [explain how subject was identified]. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

- This study is being conducted by: [Indicate University affiliation]

- Background Information:
  - The purpose of this study is: [Explain research question and purpose in lay language]

- Procedures:
  - If you agree to be in this study, we would ask you to do the following things:
    - [Explain tasks and procedures: subjects should be told about assignment to study groups, length of time for participation, frequency of procedures etc.]

- Risks and Benefits of Being in the Study:
  - The study has several risks: First, ___________________; Second, __________________ [Risk must be explained, including the likelihood of the risk]
  - The benefits to participation are:____________________________ [If no benefits, state that fact here.]
  - You will receive payment: _________________ [Include payment or reimbursement information here. Explain when disbursement will occur and conditions of payment]

- Confidentiality:
  - The records of this study will be kept private and confidential. We will store information that you give with a code number instead of your name. In any sort of report or table published, we will not include any information that will make it possible to identify a subject. Your record for the study may, however, be reviewed by the drug manufacturer or by representatives of the Food and Drug Administration. To that extent, confidentiality isn’t absolute.

- Voluntary Nature of the Study:
  - Your decision whether or not to participate will not affect your current or future relations with the University [or with other cooperating institutions, insert names]. If you decide to participate, you are free to withdraw at any time without affecting those relationships. [Explain here if monetary benefits will be adjusted due to early withdrawal]

Minors As Human Subjects

- Vulnerable population
  - Have limited ability to make informed decision
  - Can’t sign a legal document

- Participation of minor requires parent or guardian consent

- Requires minor’s assent, if minor >=7 and <= 18
  - Need to create age-appropriate materials

Do projects in this course require IRB approval?

- Active discussion at the Federal level about the need for student research to be approved by IRB
- CMU’s Federal assurance requires review of all research on campus, whether federally funded or not
- But activities are not research if they aren’t intended for building “general knowledge” (e.g., publication)
- Don’t require IRB approval
- Non-research project still require adherence to comparable ethical guidelines
  - Informed consent
  - Dealing with kids or vulnerable populations
  - Assessment of risk
Case study

- A team of computer scientists and robotics are developing software that uses machine vision to identify when a resident in a nursing home is acting violently or having a fall. To do this, they need to place cameras to capture video of residents, which will then be coded by project personnel. How do you make sure that the cognitively impaired patients understand what is happening? How should they handle video of staff and visitors? Should any areas be off-limits?

Case study 4

- In early fall 2000, Beth Israel Deaconess Medical Center (Boston) and Duke University Medical Center were the first of several health care facilities to enter into a partnership with Ardas Corporation, a biotechnology company. Ardas Corporation's stated goal is to accelerate understanding of the links between certain genetic patterns and disease, and so improve clinical applications by facilitating better diagnoses, drug development, and treatment. Ardas will create a tissue bank to provide genetic researchers with disease-specific tissues and detailed patient information to enable researchers to link specific genetic sequences with diseases such as cancer, heart disease, and neurological disorders. Ardas plans to "categorize and standardize the collection and processing of high quality clinical materials and associated information." Ardas will then provide biological materials that would otherwise be discarded as medical waste, process them into usable samples, and make them available to researchers.

  - Prior to surgery, patients will be asked by a hospital nurse if they would be willing to donate tissue samples left over from their surgery to the tissue bank. Surgeons will not know which patients have agreed, as patients will not know which patients have agreed, as the tissue bank will use a computer system to keep track of patients providing samples. All patient information will be anonymous, protected by a rigorous coding system. The hospitals will sell this tissue to Ardas. Ardas in turn will sell the patient information to biomedical researchers. Ardas will also receive license fees.

  - Although sale of human organs is illegal in the United States, no similar legal restriction applies currently to the sale of human tissues. The medical community, at this time, has not discussed extensively either the morality of selling human tissue, or, assuming that such sales are morally permissible, the question of who might have a right to share in the profits.