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Ethical Issues in Medical Physics Research
Human Subjects Research

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CHICAGO

Conflict of Interest

No conflict of interest to declare

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Objectives

Review ethical principles and regulatory requirements and a discuss cases pertaining to the protection of participants in human subject research

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Outline

- Protection of Human Subjects in Research
 - Ethical Principles
 - Nuremberg Code, Declaration of Helsinki, & Belmont Report
 - Federal Regulations
 - Common Rule & HIPAA Privacy Rule
- Case Discussions

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AAPM Code of Ethics

“Research involving human participants should adhere to the Belmont Principles of Respect for Persons, Beneficence, and Justice.”

- **Respect for persons** recognizes the autonomy of individuals and the right of each research volunteer to be treated with respect, to be fully informed about the research and its potential benefits and risks, and to be granted the ability to decide for him- or herself whether to participate in the research.
- **Beneficence** assures that some potential benefit will accrue from the research, to the participants themselves, to others with similar conditions who may benefit in the future, or to society at large.
- **Justice** means that potential participants in a study are not excluded without a valid reason for exclusion.

The screenshot shows the HHS.gov website with the following content:

- Header: HHS.gov U.S. Department of Health & Human Services
- Search bar: I'm looking for...
- Breadcrumbs: ASH > OHRP Home > Regulations > Human Subjects Research (45 CFR 46)
- Left sidebar menu: OHRP Home, About OHRP, Regulations, Human Subjects Research (45 CFR 46), Food & Drug Administration, Common Rule, Policy & Guidance, IRBs & Assurances, International, Compliance Oversight, Education, Advisory Committee (SAC/HRP), News Room, Archived Materials, Contact OHRP.
- Main heading: The Belmont Report
- Text: Office of the Secretary, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979.
- Summary section: AGENCY: Department of Health, Education, and Welfare. ACTION: Notice of Report for Public Comment. SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was...

Tuskegee Syphilis Study (1932-1974)

- U.S. Public Health Service initiated a study in AL to determine natural course of untreated, latent syphilis in black males
- Participants had agreed to be examined and treated
- They did not know they were research subjects
- They were never given adequate treatment
- 1945 Penicillin was shown to be effective for treating syphilis; they were not treated
- 1972 Study was exposed, an investigatory panel was formed, study was stopped
- 1973 Congressional hearings
- 1974, an out-of-court settlement was reached; lifetime medical benefits & burial services to all living participants
- 1995 President Clinton apologized

After Tuskegee ...

- **National Research Act** was signed into law in 1974
- Dept of Health Education and Welfare policies for the protection of human subjects were codified into law
- **National Commission** for the Protection of Human Subjects of Biomedical and Behavioral Research was formed
- Commission’s charge:
 - “to identify the basic ethical principles ... [for] research involving human subjects
 - to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.”
- **Belmont Report** in 1979

The Nuremberg Code (1947)

First international document on ethics of human subject research

1. **Voluntary consent** of the human subject is absolutely essential.
2. The experiment must yield generalizable knowledge that could not be obtained in any other way and is not random and unnecessary in nature.
3. Animal experimentation should precede human experimentation.
4. All unnecessary physical and mental **suffering and injury should be avoided**
5. No experiment should be conducted if there is reason to believe that death or disabling injury will occur
6. The **degree of risk** to subjects should never exceed the humanitarian importance of the problem
7. **Risks** to the subjects should be **minimized** through proper preparations
8. Experiments should only be conducted by scientifically **qualified investigators**
9. Subjects should always be at liberty to **withdraw** from experiments
10. 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

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Declaration of Helsinki (1964)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research
Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
 29th WMA General Assembly, Tokyo, Japan, October 1975
 32th WMA General Assembly, Venice, Italy, October 1983
 41st WMA General Assembly, Hong Kong, September 1989
 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
 64th WMA General Assembly, Fortaleza, Brazil, October 2013

- Ethical principles for medical research involving human subjects
- First adopted by World Medical Association General Assembly in 1964 (Helsinki, Finland)
- Latest amendment in Oct. 2013

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More on the history of human experimentation in the US

- ▣ Tuskegee Syphilis Study (1932-1972)
- ▣ Human Radiation Experiments (1944-1974)
- ▣ Jewish Chronic Disease Hospital Study (1963)
- ▣ Willowbrook Hepatitis Study (1963-1966)
- ▣ STD Research in Guatemala (1946-1948)

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Belmont Report (1979)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- Respect for persons
 - individuals should be treated as autonomous agents
 - persons with diminished autonomy are to be protected
 - Voluntary participation with adequate information
 - Protect vulnerable populations (prisoners)
- Beneficence
 - Maximize benefits, assess & reduce/minimize risks
- Justice
 - Fairness in selection of subjects
 - Who will receive benefits of research and who will bear its burdens
- Informed Consent
- Institutional Review Board to review/approve/monitor

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Protection of Human Subjects The Common Rule (1991)

- In US in the 1970s & 1980s federal regulations for the protection of human subjects were revised and expanded
- These regulations are codified at **45 CFR part 46**, subparts A through D
- 14 other federal departments adopted these set of rules for the protection of human subjects (also known as the **Common Rule**)

Code of Federal Regulations

TITLE 45
PUBLIC WELFARE

Department of Health and Human Services

PART 46
PROTECTION OF HUMAN SUBJECTS

Revised January 15, 2009
Effective July 14, 2009

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Protection of Human Subjects HIPAA Privacy Rule (1996)

- Required by HIPAA (Health Insurance Portability and Accountability Act)
- The Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule”)
 - establishes national standards for the protection of certain health information
- Protected Health Information (PHI):
 - “individually identifiable health information” held or transmitted in any form or media, whether electronic, paper, or oral, by a covered entity or its business associate.
- Names, addresses, dates, telephone & fax numbers, email addresses, ssn, mrn, health plan numbers, license numbers, vin, account numbers, biometric identifiers, full face photos, any other unique identifying number, characteristic, or code

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Privacy Rule

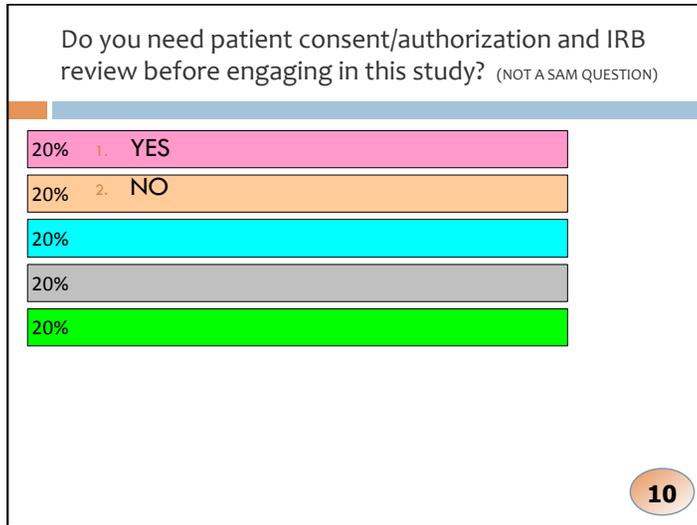
- Privacy Rule sets standards for
 - use and disclosure** of individuals’ health information —“protected health information” by organizations (“covered entities”) subject to the Privacy Rule
 - individuals’ privacy rights** to understand and control how their health information is used
- Use or disclosure of PHI allowed for Treatment, Payment and Healthcare Operations (**TPO**)
- Otherwise **Authorization** is required
- Authorization can be waived and/or altered by IRB or Privacy Board.
- De-identified** or **limited** data sets are not subject to HIPAA.

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Case 1/ A treatment planning comparison

- For whole breast irradiation, you are currently using standard tangential fields with FIF-wedge in your clinic.
- Want to explore new electronic compensation (EC) algorithm of your treatment planning system for breast planning
 - Might offer advantages (dosimetry, ease of planning, MUs)
 - If so, you might consider using it for breast planning
- A literature search reveals no published planning studies comparing standard technique and this new comp. algorithm
- You ask your resident to select 5 previously treated breast patients, re-plan using the new algorithm and compare with the standard technique

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Case 1/ A treatment planning comparison

- No mention of research.
- Could do this study as your PQI project for Maintenance of Certification (MOC).
 - Use or disclosure of PHI allowed for Treatment, Payment and healthcare Operations (TPO)
 - Quality Improvement is TPO.
- As a QI project don't need IRB review

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If we want to do research

- Research:
 - “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” 45 CFR 46.102(d)
- Is this human subjects research?
 - “ Human subject means a living individual about whom an investigator (whether professional or student) conducting research, obtains
 - data through intervention or interaction with the individual, or
 - identifiable private information” 45 CFR 46.102(f)
- Yes, a retrospective study involving a review of medical records is human subjects research

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What if the patient is deceased?

- “Human subject means a living individual” 45 CFR 46
- But...
 - “HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual.”
- Privacy Rule covers research on all human beings, living or dead.

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IRB protocol

To conduct a research involving human subjects:

- Write a research protocol &
- Submit to IRB for review/approval

What? Why? How? Who?
 Privacy & Confidentiality, Benefits, Risks
 Informed consent/Authorization

- No benefits to patients.
- Accessing patient data. Loss of confidentiality?
- De-identify/anonymize patient data.
 - Request exempt status.

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IRB response

Per our policies, use of medical record data does not typically qualify for exemption.

A. If any member of the research team will collect the data initially and then remove identifiers, the study will not qualify for exemption.

- ▣ a complete protocol submission will be needed to pursue IRB approval
- ▣ the revised submission would likely qualify for expedited review
- ▣ edit your submission as “Expedited Review” rather than “Exempt Determination” and complete the full submission form

B. If an individual not on the research team can remove all individually identifiable health information (PHI) from the research records prior to receipt by research team, the project could be considered for exemption.

Which option would you choose?

A) complete protocol submission-expedited review
 B) exempt determination (data collected & deidentified by someone else)

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Case 2/ IRB review done, but

- Contouring study done on CT image sets of cancer patients
- To study detectability of soft tissue boundaries in CT
- Various structures were contoured by physicians & physicists
- & contouring variations were analysed
- Images were obtained as part of an IRB-approved protocol

- ▣ IRB review done
- ▣ Informed Consent not mentioned
- ▣ Conjecture:
 - ▣ This could be done as a retrospective study on de-identified CT datasets
 - ▣ Consent/authorization could be removed by IRB
 - ▣ No need for IC

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Case 2/ IRB review done, but

- ▣ Informed consent from whom?
- ▣ Who are the subjects?
 - ▣ Patients—their CT images are being used
 - ▣ Physicians and physicists—whose contours are being analysed
 - ▣ Self-experimentation-if those physicians and physicists are also the authors
 - ▣ Still need IRB review
 - ▣ Assessment of risks
 - ▣ Subtle coercion

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Case 3/Informed Consent obtained, but

Study involves ultrasound imaging of participants

- Participants were patients & healthy volunteers
- **Informed Consent** was obtained from all participants

- No mention of ethics committee review

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Case 4 Ethics, institutional review and studies from private practice

COPE # 05-24

Manuscript on a chart review of a novel treatment technique, done at a private clinic

- Patients gave **informed consent** for tx; but **no ethical approval**
- Five authors, all affiliated with universities with ethics committees
- Owner/director of the private clinic who presumably has been giving the treatment, is not listed as author nor acknowledged
- Authors: ethics review not needed: private clinic, not affiliated with a university & study was a retrospective chart review
- On the clinic’s website there is a reference to a “research study” regarding this treatment, which was started nine years ago
- Retrospective chart review of the manuscript dates back to approximately the same time

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Case 4 Ethics, institutional review and studies from private practice

COPE # 05-24

Editor’s concerns:

- Prospective study with no ethical review
- Why is the clinic director not listed as author or acknowledged?

It turned out that:

- Tx was a novel application of an existing technique
- Had not previously been studied
- Was not approved for use by any ethics committee

Paper was rejected.

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Case 4 Ethics, institutional review and studies from private practice

COPE # 05-24

Would IRB review be required for this study in the US?

- Common Rule pertains to federally funded research
- But, research institutions receiving federal funding assure the government that **all** human subject research done at the institution will be conducted in accordance with the Belmont principles (Federalwide Assurance).
- This assurance covers all research involving human subjects conducted at the institution or by institution’s faculty, students, or staff.
- As such this study would be subject to IRB review.

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Case 4 **Ethics, institutional review and studies from private practice**
 COPE # 05-24

What If study is done in a private clinic, by private clinic personnel, with no University affiliation, and no government funding is involved?

- Could this treatment be allowed?
 - Yes, as off-label use, with patient consent
- Research would require consent/authorization (HIPAA).
- There still is ethical obligation for a review process (Belmont Report & Helsinki Declaration)

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Case 3 again/Informed Consent obtained, but

Study involves ultrasound imaging of participants

- Participants were patients & healthy volunteers
- **Informed Consent** was obtained from all participants

- No mention of ethics committee review
 - How will **incidental findings** in healthy volunteers be handled?

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Incidental Findings

Findings unrelated to the clinical indication for the test/procedure/ imaging examination performed

How to manage these “incidentalomas”

- ▢ Uncertainty, anxiety, risks, costs

In a research setting:

- How to protect subject welfare and research integrity
- Subject expectations
- Informed consent
- Professional training of the research team
- Burden of false-positives
- Financial cost of follow-up

“Incidental Findings in Brain Imaging Research: What should happen when a researcher sees a potential health problem in a brain scan from a research subject? J. Illes et. al., Science, 2006 February 10; 311(5762): 783–784.

IF in Rad Onc **UNSUSPECTED ABNORMALITIES NOTED ON CT TREATMENT-PLANNING SCANS OBTAINED FOR BREAST AND CHEST WALL IRRADIATION**

VIVEK K. MEHTA, M.D. AND DON R. GOFFINET, M.D.
 Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA

153 patients referred for breast or chest wall radiation therapy

- ▢ Tx planning scans included neck, thorax, liver
- ▢ A resident & attending reviewed each scan
- ▢ Any abnormal findings were reviewed by a radiologist
 - ▢ additional diagnostic imaging or other evaluation was obtained as needed
- ▢ 17 unsuspected abnormalities were noted in 153 scans (11%)
 - ▢ 4 were additional cancer foci (3%) & altered the treatment plan

Int. J. Rad. Oncology Biol. Phys., V49, No. 3, pp. 723–725, 2001

Back to Case 1, breast planning study...

We had patient data anonymized by a colleague not in the research team to get exempt status

- ▣ What if the keen rad onc resident in your research team notices a suspicious nodule of the kind found in this paper on incidental findings in breast irradiation?
 - An IF is found, what would you do if the data are fully anonymized
 - In view of possibility of IF, should you even anonymize the dataset
- ▣ Should incidental findings be a concern and discussed and addressed in the IRB protocol for this retrospective study?

Case 5/ Research with healthy volunteers

Healthy volunteers are placed on a linac couch and imaged with ultrasound while gantry is rotating

- IRB review or Informed Consent not mentioned
 - Volunteers could be the authors themselves
 - Self-experimentation, vulnerability (of junior researchers)

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Research with Volunteers The Ellen Roche Case (2001)

- Ellen Roche was a healthy 24 y.o. lab technician in asthma and allergy center at Johns Hopkins University
- Participated in an asthma study as a volunteer (2001)
- Took a drug and inhaled hexamethonium to simulate an asthma attack
- Developed a cough, was hospitalized 4 days later
- Died in the ICU after several weeks
- The consent form did not mention risks
 - Studies going back 50 yrs did not indicate harm
 - But papers from 1950's reported hexamethonium could cause fatal lung inflammation

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Summary

- Human subjects research requires institutional review board/ethics committee review & informed consent
- Increasingly journals require that IRB/ethics committee review & informed consent are explicitly stated in the manuscript
- It is not always clear who the research subjects are
 - Researchers themselves may be subjects
 - This still requires IRB-review and consent
 - Healthy volunteers might be subjects
 - Issue of Incidental findings need to be addressed
- Incidental findings might need to be addressed in retrospective studies on patient data as well

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SAM QUESTION 1. Three basic ethical principles of the Belmont Report pertaining to research involving human participants are

- 20% 1. Respect for Personal Autonomy, Beneficence, Justice
- 20% 2. Respect for Persons, Beneficence, Justice
- 20% 3. Respect for Persons, Informed Consent, IRB Review
- 20% 4. Respect for Persons, Non-maleficence, Justice
- 20%

10

The answer is

- 2. Respect for Persons, Beneficence, Justice

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SAM QUESTION 2. Common Rule refers to the regulations, set forth for the protection of human participants in research,

- 20% 1. common to all member states of the United Nations
- 20% 2. in countries complying with Helsinki Declaration
- 20% 3. in the United States
- 20% 4. common to United States and Canada
- 20%

10

The answer is

- 3. in the United States

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SAM QUESTION 3. With regard to federal regulations on research involving human participants, which of the following statements is TRUE:

- 20% 1. IRB review and IC are required for all biomedical research
- 20% 2. Common Rule pertains to the protection of living research participants
- 20% 3. Privacy Rule does not protect the health information of deceased persons
- 20% 4. IRB review and IC are required for all research involving human subjects

20%

10

The answer is

- 2. Common Rule pertains to the protection of living research participants

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