You be the IRB: Case Studies in Human Research Protection

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Learning objectives

- Discuss history of human subject research regulations
- Learn about IRB regulations and role in protecting human subjects
- Review case studies in an IRB meeting

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What Is an IRB?

- An IRB is an Institutional Review Board – a board composed of scientists (MD and non-MDs) and non-scientists who review non-exempt human subjects research according to a set of criteria called the 45 CFR 46.111 criteria
- An IRB must have at least 5 members "with varying backgrounds" and must include an unaffiliated member
  - Nonscientist required for quorum

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What Is an IRB?

REGULATIONS

ETHICS

RESEARCH

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Why do we have IRBs?

- The IRB review process was established in direct response to research abuses during the 20th century.
- Various "trigger events" resulted in legislative and ethical responses, culminating in the creation of human subject research regulation and IRBs.

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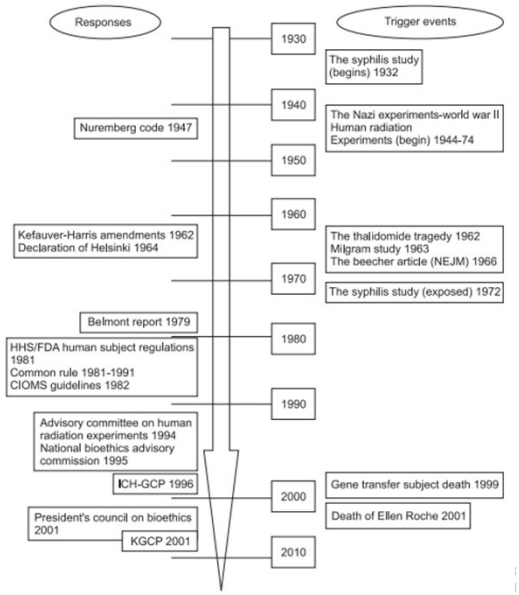

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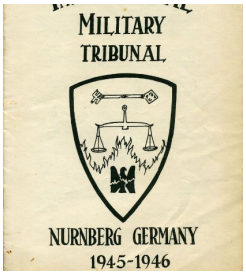
Why do we have IRBs?

- The modern history of human subjects protections begins with the Nuremburg Code



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TRIGGER EVENT: WWII

- ❑Nazi Germany
- ❑Targeted POW and minority populations to improve battlefield medicine
- ❑Exposure to extreme conditions, surgeries, deliberate infections with pathogens

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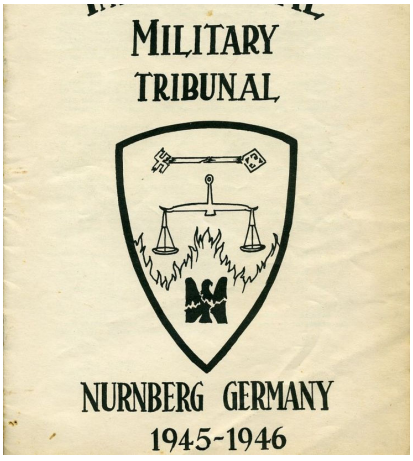
RESPONSE: NUREMBERG CODE

- December 1946 to August 1947
- 23 doctors/scientists put on trial
- The Nuremberg Military Tribunal developed 10 principles to define legitimate medical research, to judge the Nazi doctors.
- Main Takeaways:
  - Voluntary consent of subject is essential
  - Sound scientific research design
  - Risks should be minimized and reasonable in relation to benefits



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Nuremburg Code

- The voluntary consent of the human subject is absolutely essential.
- The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
- The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
- The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
- No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
- The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
- Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
- The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
- During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
- During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

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RESPONSE: DECLARATION OF HELSINKI 1964

WORLD MEDICAL ASSOCIATION

Cornerstone document for human research ethics

- Undergoes updates

- ➢Introduces the idea of an Independent committee
  - ➢Ethical determinations removed from the physician/investigator and shifted to an independent body
- ➢Consent regulations “relaxed”
  - ➢LAR consent permitted
- ➢Re-emphasis on risk/benefit ratio
  - ➢Including analysis during study

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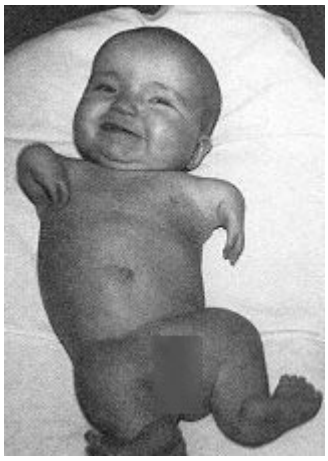

TRIGGER EVENT: Thalidomide

- First marketed in Europe
- Marketed as a sleeping aid/anti-emetic for pregnant women
- Caused severe and often fatal congenital abnormalities
- Frances Kelsey from the FDA tried to keep it off the market, requesting information on safety
- In response, Merrell starts marketing aggressively to doctors for "experimental use"
- FDA vs Industry - Merrell withdraws its New Drug Application

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RESPONSE: KEFAUVER-HARRIS AMENDMENTS 1962

- Strengthen the role of Government/FDA in the research process
- Demand "substantial evidence of efficacy"
- Full and Free Consent of all participants in Drug Trials in the US and reporting of adverse events

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TRIGGER EVENT:

Tuskegee Syphilis Study

- Undertaken by US Public Health Service to study the untreated effect for syphilis
- 1932 – 1972

❑600 African American Men in rural Alabama
❑Incentives free meals, free medical exams, and free burial costs
❑Unaware of their disease status
❑1951 Penicillin available
❑NYT breaks the story in July 1972

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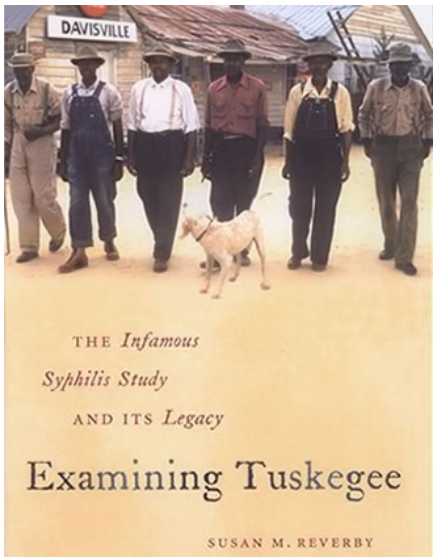

Tuskegee

- No informed consent, no treatment given once discovered, no opportunity to withdraw
- AP article led to Advisory Panel, which shut down study

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Why do we have IRBs?

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974

- Tasked with developing guidelines for human subject research and to oversee and regulate the use of human experimentation in medicine.
- Issued the Belmont Report in 1979
- Formalized IRB regulations

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Why do we have IRBs?

Belmont Report

The three fundamental ethical principles for using any human subjects for research are:

- Respect for persons: autonomy and informed consent
- Beneficence: "do no harm"; maximize benefits and minimize risk.
- Justice: equitable selection; fair distribution of costs and benefits

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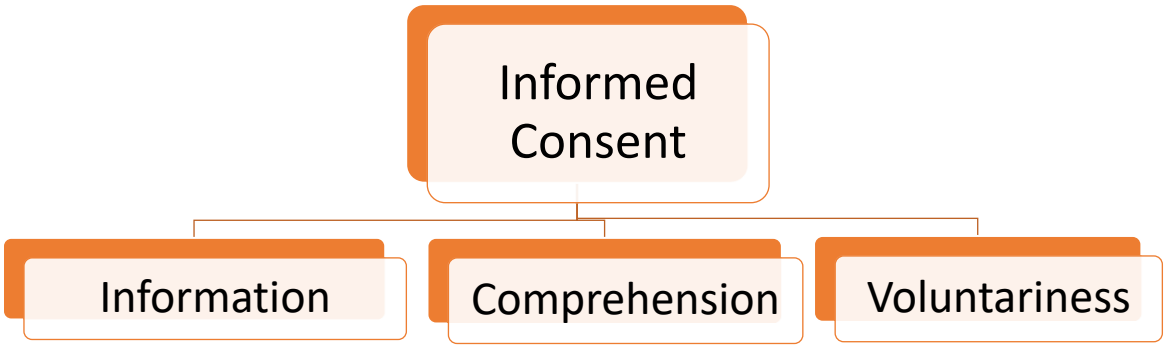
RESPECT FOR PERSONS IN PRACTICE



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Research Regulations

45 CFR 46 in the Code of Federal Regulations: "Common Rule"

- Originally adopted January 13, 1981
- Revised June 18, 1991
- Revised in 2018 ("The New Rule")

- USA regulations governing biomedical and behavioral research involving human subjects
- Detailed guidelines IRB's need to follow to approve human subjects research

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Definitions

Research: 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:

- (i) About whom a researcher obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

- (ii) About whom a researcher obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens; or

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Research Regulations

"Common" Rule has IRB approval criteria at 45 CFR 46.111:

- Risks need to be minimized: use of sound procedures and design
- Risk/benefit ratio: Weighing direct benefit to subject in relation to the risks of the research. Societal benefit is also factored in.
- Equitable selection: purpose and setting of research, mindful of vulnerable subjects. IRB must be cognizant of vulnerable populations. Fair distribution of burdens and benefits.

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Research Regulations

- Consent process: are all elements of consent included in the consent document? Is the information presented in an understandable way to subject or LAR?
  - The IRB also determines whether consent can be waived if it meets five criteria:

Waiver of Informed Consent:

(i) The research involves no more than minimal risk to the subjects;

(ii) The research could not practicably be carried out without the requested waiver or alteration;

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

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Research Regulations

- Documentation of consent: consent will be appropriately documented. Waiver of documentation of consent can be requested, provided it meets one of the two criteria.
- Data & Safety Monitoring: When appropriate, there is a monitoring plan in place for monitoring data to ensure the safety of subjects.
- Privacy and Confidentiality: plan in place to protect privacy of subjects and maintain the confidentiality of data.
- Vulnerable populations: additional safeguards need to be in place to reduce coercion or undue influence and protect vulnerable pops.

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.111 Criteria and the Belmont Report

1. Risks minimized. BENEFICENCE
2. Risks reasonable in relation to benefits. BENEFICENCE
3. Selection of subjects is equitable. JUSTICE
4. Informed consent process. RESPECT FOR PERSONS
5. Informed consent documentation. RESPECT FOR PERSONS
6. Adequate monitoring of data. BENEFICENCE
7. Protect privacy/maintain confidentiality. BENEFICENCE
8. Safeguard vulnerable populations. RESPECT and JUSTICE

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Vulnerable Populations

The Common Rule has regulations covering 3 "vulnerable populations". Provides additional safeguards for these populations while allowing important research to proceed.

Subpart B: Pregnant Women, human fetuses, and neonates

Subpart C: Prisoners

Subpart D: Minors

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Vulnerable Populations

Subpart B: Pregnant Women, human fetuses, neonates of uncertain viability, or nonviable neonates.

Informed Consent:

- It specifies when and how informed consent should be obtained from the pregnant woman, and in some cases, the father, for research involving the fetus or neonate.

- **Risk/Benefit Assessment:**
  - Subpart B outlines different risk considerations for research involving fetuses and neonates, requiring potential for direct benefit for research with more than minimal risk to fetus. Must assess risk to fetus separately from risk to pregnant woman.
- **No Inducements:**
  - It prohibits the use of monetary or other inducements to terminate a pregnancy for research purposes.
- **No Involvement in Termination Decisions:**
  - Individuals involved in the research are prohibited from participating in decisions about the timing, method, or procedures for pregnancy termination.

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Vulnerable Populations

Subpart C: Prisoners

- **Goal:** Mitigate risk of coercion or undue influence due to incarcerated status, promote voluntariness
- **IRB Review:**
  - The IRB reviewing research with prisoners must include a prisoner or prisoner representative, among other requirements.
- **Permissible Research Categories:**
  - Subpart C outlines specific categories of research that are permitted with prisoners, including studies on the causes and effects of incarceration, prisons as institutions, conditions particularly affecting prisoners, and research aimed at improving prisoner health and well-being.

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Vulnerable Populations

Subpart D: Children

- **Parental Permission and Child Assent:**
  - Researchers obtain permission from the child's parents or guardians, and also seek the child's assent to participate, when appropriate based on the child's age and maturity. Waiver of parental permission also an option.
- **Risk Categories:**
  - Research involving children is categorized based on the level of risk (and based on those levels, either one- or two-parent consent may be required)
- **Additional Protections:**
  - Subpart D also addresses specific situations, such as research involving children who are wards of the state, requiring additional protections in those cases.

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Exempt Research

- Federal and institutional-specific categories for pre-determined “minimal risk research”; ex:
  - Educational research
  - Surveys/interviews/focus groups
  - Benign behavioral interventions
  - Secondary use of data
- How do we protect?
  - IRB needs to make initial exempt determination
  - Privacy/confidentiality considerations
  - “Abbreviated consent” when subject interaction

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Exempt Human Subjects Research Informed Consent

Abbreviated (Exempt) Consent Elements

- that this is a research study; and
- participation is voluntary; and
- the purpose; and
- what the subjects are being asked to do; and
- confidentiality protections; and
- how long participation is expected to take; and
- a disclosure if the subject will be audio- or video-taped; and
- how to contact an investigator or research staff member for questions about the study.

No signature needed, unless protected health information (PHI) is collected

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Not Human Subjects Research (NHSR)

Human subject: a living individual about whom an investigator conducting research obtains:

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Common types of research with NO human subjects:

- Analysis of publicly available data (data is not 'private information')
- Analysis of anonymous datasets; for example, from CDW (data is not identifiable)
- Laboratory science with non-identifiable samples

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IRB Agenda

1) A professor wishes to conduct a study about the student experience using ChatGPT. He teaches 3 full classes, and so he thinks it should be relatively easy to fulfill his study sample size in a short period of time. He plans to introduce the study in-person in class, and conduct a group consent process after passing out the Exempt Information Sheet. Once his students have consented to participate, he will provide them with the link to the survey study.

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- Respect for Persons; (4) Informed Consent (though exempt)
- Justice; (3) Equitable selection

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IRB Agenda

2) A student researcher plans to conduct a one-time interview study with individuals with substance use disorders and history of incarceration. She needs to collect their names and phone numbers in order to schedule the interviews. She plans to label the Zoom audio-recordings and associated transcripts with this contact information, in case she decides she needs to follow up with them for more information at a later date. As she may graduate BU before she finishes the study, she plans to store these data on her laptop in her personal Google Drive instead of using the institutional platform, as she does not wish to lose access to these data once her BU affiliation ends.

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- Beneficence; (7) Adequate confidentiality protections

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IRB Agenda

3) A pediatrician is planning to conduct an observational study with patients that she sees in her clinics. The study involves research blood draws and surveys every 6 months. She sees patients ages 14-17 years of age in her clinic, though she needs to follow them in the study until they are 21. In order to enroll them into this study, she plans to conduct a one-time consent process with their parent, since they will be minors at the time of enrollment.

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- Respect for Persons; (4) Informed Consent

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IRB Agenda

4) Pharmaceutical Company XYZ is planning to conduct an early-stage clinical trial to test a new investigational drug that they hope reduces viral load in HIV+ patients. They believe that it will be difficult to enroll patients in the United States, since there are already effective drugs on the market, and most US-based patients who are HIV+ will already be taking one of these approved medications as part of their standard care. They decide to conduct their study in a foreign country where use of the existing approved drugs is much less common. While they have no current plans to market the drug in this country if the trial is successful and the drug eventually obtains FDA approval, they think it will be easier to hit their enrollment targets by conducting the study in this location.

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- Justice; (3) Selection is Equitable

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IRB Agenda

5) Medical Device Company ABC wants to develop a non-invasive device to measure brain blood flow in patients who have suffered recent severe head trauma. Many of these patients are comatose, but have regular visits from their family. The device itself presents minimal risk, using probes that emit light. In order to obtain the data needed to answer the study question, the investigational device needs to be placed within 7 days of hospital admittance. Because the patient cannot provide consent due to their cognitive condition, the company plans to ask the hospital clinic staff treating the patient to allow them to use the device to collect data two separate times when the clinic staff is not actively treating the patient.

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IRB Agenda

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- Respect for Persons; (4) Informed Consent

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IRB Agenda

6) A vascular surgeon wants to conduct a review of medical records to look at post-operative pain following peripheral artery bypass using one standard surgical technique vs. another. They plan to look at 100 medical records from 2010-2020 to extract data about health status pre-bypass, any surgical complications, post-operative clinic visit data, pain-scale results, and use of analgesics. To characterize the population, the surgeon will also extract for each subject home address, employment status, citizenship status (documented or undocumented), and health insurance status.

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IRB Agenda

6) A vascular surgeon wants to conduct a review of medical records to look at post-operative pain following peripheral artery bypass using one standard surgical technique vs. another. They plan to look at 100 medical records from 2010-2020 to extract data about health status pre-bypass, any surgical complications, post-operative clinic visit data, pain-scale results, and use of analgesics. To characterize the population, the surgeon will also extract for each subject home address, employment status, citizenship status (documented or undocumented), and health insurance status.

- Beneficence; (1) & (2) Risks are minimized

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IRB Agenda

7) A physician is an expert in a rare neurodegenerative disorder. Due to the rarity of the disease, patients fly in from across the country to be seen in her clinic. She plans to conduct a chart review study, evaluating her patient records from 2011-2030 to track the treatment success of the clinical medication regimen she has developed. As she will only be looking at medical records, and not conducting any research-only procedures with her patients, she does not plan to obtain signed consent.

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IRB Agenda

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- Respect for persons; (4) Informed Consent

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IRB Agenda

8) A pharmaceutical company plans to conduct a clinical trial in patients who have an active seizure while in the hospital. The investigational study drug is given as a one-time infusion during the seizure. They plan to only enroll patients who have a legally authorized representative (LAR) available who can consent on the behalf of the patient, since the patient will not have capacity. The only research activity that involves enrolled participants is the infusion of the study drug. In order to limit participant burden, they do not plan to conduct any follow-up visits or phone calls with the participant or LAR. Instead, to evaluate the outcome of the treatment with the investigational drug, the company will request the length of stay in the hospital for each participant from the hospital medical records.

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- Beneficence; (6) Adequate provisions for monitoring safety data

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IRB Agenda

9) An investigator needs fresh blood samples from healthy individuals to conduct tests in his lab. He does not need any identifiers nor any clinical information, but the blood needs to have been drawn within 24 hours. As he only needs a one-time draw of 20mL from each participant, he reasons that the study is minimal risk. He plans to recruit the postdocs in his lab by emailing them the IRB-approved consent form for them to electronically sign in REDCap.

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Justice; (3) Equitable selection of subjects

Respect for Persons (autonomy); (4) Consent

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IRB Agenda

10) An investigator plans to conduct a study that involves taking extra liver biopsy samples during a clinical hepatectomy in patients with liver cancer. They will screen the surgical schedule under a waiver of HIPAA authorization, and approach patients for the consent discussion in the waiting room when they come in on the day of surgery. While they imagine that most of the tissue will be needed for their experiments, they also hope to retain any extra tissue in a repository for unspecified future use. The exact plans for the future use is unknown, so the consent form solely focuses on explaining how the tissue will be used in this study.

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IRB Agenda

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Respect for Persons; (4) Consent

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Oversight Needs to Remain Ongoing

New York State Psychiatric Institute (2023):

- Participant in a study testing a Parkinson's drug (Levodopa) for late-life depression died by suicide while enrolled in NIH-funded study
- OHRP suspends all federally-funded research at the institution
- FDA audit finds:
  - IRB did not report UP (suicide) nor serious noncompliance determinations to FDA
    - Failure to follow protocol, failure to report AEs, failure to document eligibility, enrolling ineligible subjects, etc
  - IRB did not have appropriate quorum during reviews
    - No nonscientists

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RESOURCES

Belmont Report:
https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Common Rule:
https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

BUMC/BMC Policies and Procedures:
http://www.bumc.bu.edu/ohra/hrpp-policies/

Beecher, HK. (1966). N Engl J Med 1966; 274:1354-1360
DOI: 10.1056/NEJM196606162742405

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Thank you!

What Questions Do You Have?

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