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Ethical Oversight of Human Subject Research

Funding was provided through a Community Engagement Supplement to the Oregon Clinical and Translational Research Institute at Oregon Health & Science University (National Institute of Health/NCRR/NCATS grants UL1TR000128 and ACTRI0601).

Mandate of the IRB

- Review all research involving human subjects performed by OHSU faculty, research staff, and students
- Charged with the responsibility to protect the rights and welfare of human subjects who are recruited or otherwise participate in research activities conducted under the auspices of the University
- Committed to protecting the confidentiality, privacy and security of health information collected in the research context

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Belmont Report

- The Belmont Report expresses the duties that investigators have to research subjects in terms of three ethical principles:
  - Respect for Autonomy – recognition of a person's right to self-rule and dignity; special protections for those with diminished capacity.
  - Beneficence – the obligation to maximize benefits and reduce or eliminate harms.
  - Justice – the fair distribution of burdens (risks) and benefits in research.

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Common Rule

- The Common Rule
  45 CFR 46
- OHRP & FWA
  (Office for Human Research Protections & Federal Wide Assurance)
- 21 CFR 50,56- FDA

  (Food & Drug Administration)

- 7 CFR part 1c Department of Agriculture
- 10 CFR part 745 Department of Energy
- 14 CFR part1230 National Aeronautics and Space Administration
- 15 CFR part 27 Department of Commerce
- 16 CFR part 1028 Consumer Product Safety Commission
- 22 CFR part 225 Agency for International Development
- 24 CFR part 60 Department of Housing and Urban Development
- 28 CFR part 46 Department of Justice
- 32 CFR part 219 Department of Defense
- 34 CFR part 97 Department of Education
- 38 CFR part 16 Department of Veterans Affairs
- 40 CFR part 26 Environmental Protection Agency
- 45 CFR part 46 Department of Health and Human Services
- 45 CFR part 46 Central Intelligence Agency
- (by Executive Order 12333)
- 45 CFR part 690 National Science Foundation
- 49 CFR part 11 Department of Transportation

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Requirement of Compliance - FWA

No Universal Law on Protection of humans in research

It is tied to funding:

Each institution engaged in research covered by

45 CFR part 46 and which is conducted or supported

by HHS (or other federal funds) shall provide assurance satisfactory to the HHS Secretary that it will comply with the requirements set forth in

45 CFR part 46 [45 CFR 46.103(a)].

Federal-Wide Assurance = FWA

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Human Subject: Definition 46.102(f)

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.

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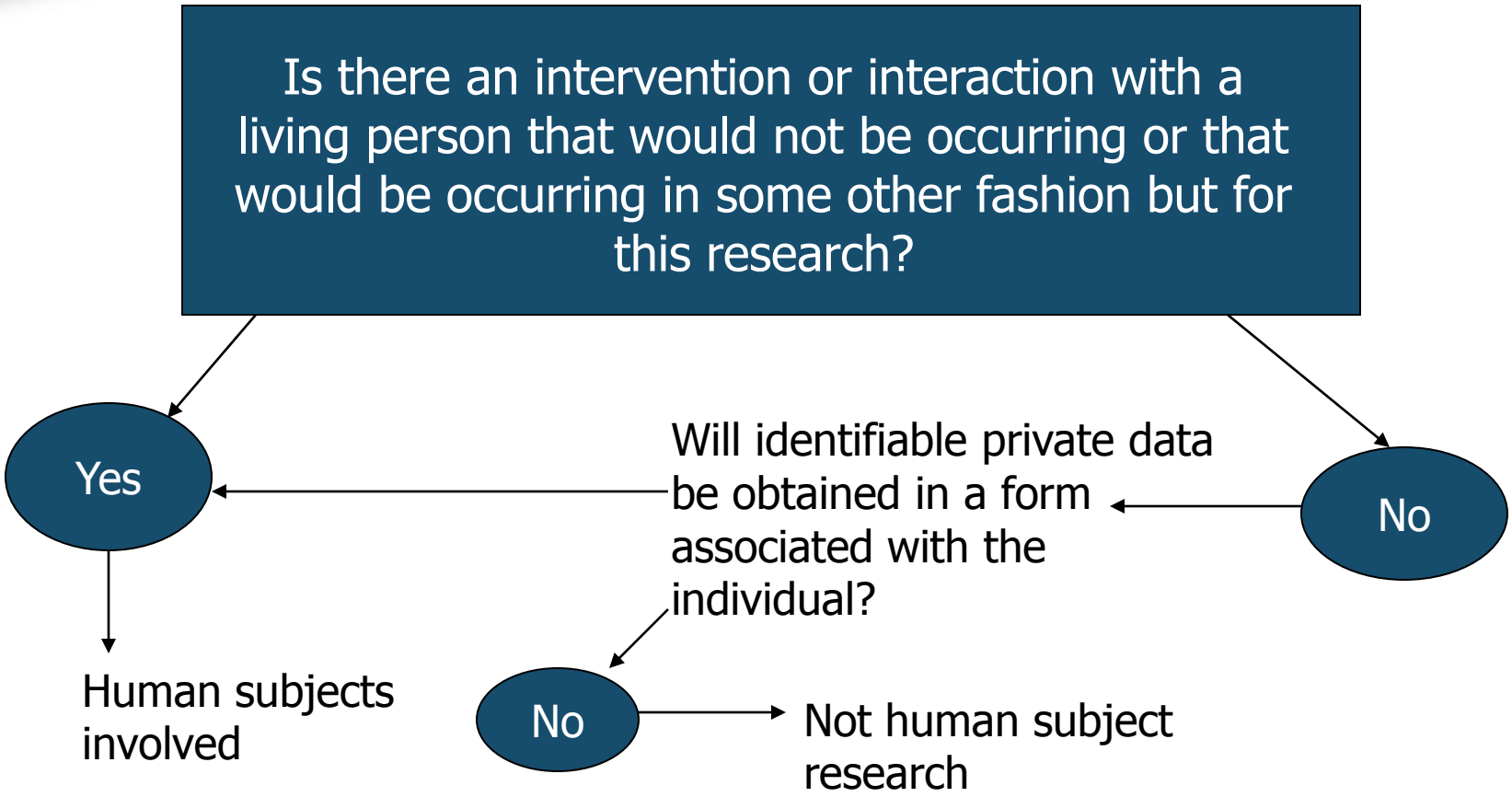
Human Subject: Definition 46.102(f)



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What is NOT a Human Subject?

- **Data on Deceased Individuals** (does not meet human subject definition – but is HIPAA regulated)

- **Use of existing data under the following conditions ONLY:**
  - No interaction with a human,
  - Data exists at time of IRB application,
  - Investigator will not be given access to identifiable data,
  - Data does not contain personal identifiers, and
  - A list is not maintained by anyone that can connect the data with personal identifiers or an agreement exists not to share the code-breaker

Example: Investigator A at Institution A has identifiable data that s/he has collected for research. Investigator B at institution B wants to use the data for research purposes. Investigator A sends investigator B the data with all identifiers stripped. A list is not kept by anyone who can connect the data with the names of individuals.

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Human Subject YES! *Perhaps Exempt.*

If investigator will have access to identifiable data but the investigator **does not** record any identifiers, the activity involving use of the data is human subjects research that must be submitted to the IRB for certification of exempt status.

Example: Investigator A at institution A has identifiable data that s/he has collected for research. Investigator B at institution B goes to institution A and records the data s/he would like to use but s/he does not record any identifiers.

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What is Research?

- **46.102** (d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

- NIH Definition: Research involving human subjects is an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).

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Gray Areas

Practice vs. Research

Public Health Surveillance? Quality Assessment? Case Reports?

Questions to consider:

- Will the results be generalizable beyond the population being served?
- Is the intent to generate new knowledge or improve upon an existing principle, theory or knowledge?
- Is the intent to publish or present the results to the scientific community?
- Activities which meet the definition constitute research, 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.

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Issues in Research Design

- IRB Review and Considerations
- Informed Consent
- Collaboration - Engagement in Research
- Equipoise – uncertain that 1 arm is better than the other
- Safety Monitoring
- Special Groups – Vulnerable Populations
- Investigator Compliance

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IRB Review Considerations - 46.111

- Risks to subjects are minimized:
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
- Selection of subjects is equitable
- Appropriate Informed consent will be sought from each prospective subject or the subject's legally authorized representative
- Informed consent will be appropriately documented
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

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Vulnerable Populations

- Some classes of research subjects are considered to be more vulnerable to coercion and in need of additional protections. These include:
  - Children
  - Persons with Reduced Capacity
  - Prisoners
  - Fetuses and Pregnant Women
  - Terminally Ill
  - Students
  - Employees

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Informed Consent Process Requirements

- Statement that the study involves research
- Explanation of the purposes of the research
- Expected duration of the subject's participation
- A description of the procedures to be followed
- Identification of experimental procedures
- Foreseeable risks or discomforts to the subject
- Benefits (if any)
- Alternative procedures available
- Confidentiality of records
- No Exculpatory Statements
- Reduce Coercion or undue influence
- participation is voluntary

If applicable
(greater than minimal risk):

- explanation of compensation and treatment in the case of injury
- whom to contact for questions
- refusal to participate will not involve loss of benefits

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Definition of Minimal Risk

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 46.110

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Children's Issues

- ☐ Categories of Approvable Research [45 CFR 46.404-7]
- ☐ Soliciting consent or assent [45 CFR 46.408(a)]
- ☐ Soliciting permission of each parent or guardian (one sufficient for 46.404 or 405) [45 CFR 46.408(b)]
- ☐ Waiver of parental or guardian permission [45 CFR 46.408(c)]
- ☐ Protections for wards of state or any other agency, institution or entity for research approved under 46.406 or 407 [45 CFR 46.409]
- ☐ Research in Schools

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Certificates of Confidentiality

- A major impediment to enrolling subjects in some types of research is the fear of loss of confidentiality of sensitive information.
- Certificates of Confidentiality (issued by DHHS) protect against compelled disclosure in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding.
- No cases of successful subpoena of CoC protected information.
- Common Uses:
  - Substance abuse
  - Sexual attitudes/practices
  - Illegal behaviors (not drug-related)
  - HIV status
  - Psychological well-being
  - Domestic violence

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Investigator's Role

- Primary responsibility for protecting the rights and welfare of human subjects
- Complying with provisions of Assurance
- Knowledgeable about human subjects regulations, State and local laws, Assurance and institutional policies and procedures
- Conducting research according to IRB-approved protocol
- Complying with all IRB determinations
- Ensuring that potential subjects understand the research
- Providing a copy of the IRB approved consent document to each subject or legally authorized representative, unless waiver or alteration granted by IRB
- Maintaining consents according to IRB requirements
- Promptly reporting proposed changes in IRB-approved research prior to initiation of the change, except to eliminate apparent immediate hazards to subjects
- Reporting progress according to IRB requirements
- Promptly reporting to the IRB any unanticipated problems involving risks to subjects or others

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IRB

- Composed of at least 5:
  - qualified OHSU faculty and community members
  - at least one member who is not affiliated with OHSU
  - at least one member who has no medical or scientific background
  - Varying genders and ethnicities
- Members appointed by the Provost for 3 years with option to renew
- Has final authority to disapprove research
- Currently 4 committees
- Members cannot vote or be present for the vote on their own protocols (recusal)

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IRB – Review

- IRB decisions:
  - Approve as presented
  - Approved with required administrative changes.
  - Deferred – substantive concerns regarding proposal.
  - Disapproved.

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Some Case Studies

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Case: Gelsinger v. U. of Penn.

- Jesse Gelsinger was an 18 yeal old with a mild case of ornithine transcarbamylase deficiency (OTC).
- P.I. Was U. Penn investigator who was also founder of Genovo, Inc.
- P.I. gave Jesse an experimental genetic therapy using a viral vector. He died from multiple organ failure secondary to virus.
- Allegations:
  - Exclusion Criteria
  - Adverse Events in monkeys and other subjects
  - Consent lacked sufficient animal testing data;
  - Consent lacked sufficient alternative information;
  - Consent failed to mention that PI had a 30% equity in the sponsor company ($13.5 million).

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Case: Ellen Roche & Johns Hopkins University

- Ellen Roche was a healthy volunteer for a JHU asthma study. Ms. Roche was given hexamethonium to simulate asthmatic conditions. She developed respiratory distress and, within days, died of multiorgan failure. No lawsuit was filed but JHU reached an undisclosed financial settlement with Ms. Roche's family.
  - PI did not follow approved protocol for drug preparation
  - Drug required an IND
  - Ellen was an employee
  - Failure to report persistent cough as unexpected adverse event.

Case: Grimes v. Kennedy Kreiger

- Non-therapeutic experiment on children, done with their parents consent.
- Varying levels of lead abatement
- Claimed that KKI did not fully inform of risks and contributed to increased lead levels
- Found
  - Consent form had contract elements
  - Researcher has special duty to volunteers
  - Parents consenting to greater than minimal risk, no prospect of direct benefit.

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Catalona v. Washington Univ.

- Prostate Cancer Repository
- PI Changed institutions and sought permission from participants to take samples with him. (Moore v. Reagents of UC)
  - Court held WU had ownership of samples under gift law.
  - Appealing to Supreme Court under 45 CFR 46.116, “No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights..”

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Havasupai v. Arizona State

- collected 400 blood samples from tribal members for diabetes research.
- those same samples were shared and used for additional unauthorized research on schizophrenia, inbreeding, and population migration.
  - The tribe asserts that research on schizophrenia and inbreeding sitgmatizes them and that they would not have authorized any migration research because it conflicts with their religious origin story.
  - Consented for genetic testing to identify an association between certain gene variants and diabetes among Havasupai people

Bearder v. Minnesota

- Heel prick Blood samples collected by MPH for public health practice – disease surveillance
- (2008) A group of families sued the Minnesota Department of Health (MDH) for collecting blood samples from newborns for a newborn screening program and without parental knowledge or consent, retaining the samples indefinitely, and sharing the samples with private research institutions and hospitals. Minimal Risk

Beleno v. Texas Dept. of Health, Texas A&M

- As part of public health practice, disease surveillance, since the 60's TX has collected newborn blood samples. (heel prick)
- Since 2002, have held for research. Minimal Risk.
- In 2006, contracted with Texas A&M to store the samples
- 2009, case brought by group of parents, working with Texas Civil Rights Project, challenging state's retention of samples for future undisclosed research.

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Thank-you.

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