Foundations in Ethical Research GRAD214

UCSF Winter/Spring 2025

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Please answer the following

I work with human subjects

0%

I work with human biospecimens

0%

I work with with animals

0%

I do not work with humans, human biospecimens, or animals

0%

Protection of Human Subjects in Research

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The Protection of Human Subjects

- Know what types of research are subject to regulation
- Understand and follow the rules for project approval
- Get appropriate training
- Accept continuing responsibility for compliance

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A Little History

- Welfare of research subjects was not protected until after World War II
  - Widespread concerns about atrocities committed
- Nuremberg Code (1947)
- Declaration of Helsinki (1964)
  - Latest revision and clarification, 2013
  - First international guidelines for the ethical treatment of human subjects

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Nuremburg and Helsinki Were Not Enough

- **Cold War**: radiation experiments on hospital patients, children, and soldiers without informed consent
- **Tuskegee Study** (1932-1972): African-American males in a long-term syphilis study not offered penicillin once discovered in 1945
- **Willowbrook State School** (1963-1966): mentally disabled children intentionally infected with viral hepatitis

Here Comes the Regulation…

- 1974 Congress enacted the **National Research Act** requiring HHS to clarify rules for human subjects in research
  - Established the **Belmont Report** in 1979
  - Federal Policy for the Protection of Human Subjects codified as **45 CFR 46**
- FDA codified its rules for human subjects research
  - **21 CFR 50 and 56**
- Expected to harmonize soon

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1979 Belmont Report

- **Respect** - the right to make decisions for and about themselves without undue influence or coercion from someone else
- **Beneficence** - to maximize benefits and reduce risks to the subject
- **Justice** - to distribute benefits and risks equally without prejudice to particular individuals or groups

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Federal Policy becomes the "**Common Rule**"

- 1991 - Adopted by 20 Federal departments and agencies
- Additions to 45 CFR 46:
  - Subpart B – Pregnant Women, Human Fetuses, and Neonates
  - Subpart C – Biomedical and Behavioral Research Involving Prisoners
  - Subpart D – Children as Research Subjects
  - Subpart E – Registration of IRBs with HHS
- Subparts not considered Common Rule as some Federal agencies have their own rules for vulnerable populations

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Common Rule Definition of Research

- "**Systematic investigation**, including research development, testing and evaluation, designed to develop or **contribute to generalizable knowledge.**"
- A project or study is research:
  - Conducted with the intention of drawing conclusions that have some general applicability
  - Uses a commonly accepted scientific method

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Is this Research?

A team of physicians sees a patient with an unusual constellation of symptoms. They run a variety of diagnostic tests and procedures. Results of the test do not yield a known diagnosis.

They write a case summary of their observations and submit it to a medical journal for publication.

Answer: No

Is this Research?

The same group of physicians identified several case reports in the medical literature of patients with similar disease presentations. They have a hypothesis, that these patients suffer from the same disease. They want to systematically review these cases to identify characteristics and commonalities that would help them better understand this disease – thus contributing to generalizable knowledge about the disease

Answer: Yes

Definition of a Human Subject

- Human subjects are "**living** individual(s) **about whom** an investigator conducting research obtains data through **intervention** or **interaction** with the individual or uses **identifiable private information**"
- Humans are considered subjects:
  - Researcher interacts or intervenes directly with them
  - Identifiable private information is collected
- Institutional approval is needed before any work is undertaken

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Does the Research Involve Human Subjects?

A researcher hypothesizes that some middle-aged women who died from COVID-19 had undiagnosed or untreated underlying heart disease. To investigate the hypothesis, the researcher plans to systematically review identifiable medical records of 400 deceased women ages 45-65 who were hospitalized with COVID-19 to look for commonalities like high blood pressure, high LDL, etc.

Research: Yes

Research that involves human subjects: No

Does the Research Involve Human Subjects?

A researcher hypothesizes that children who attend pre-kindergarten with rigorous academic instruction present with behavioral issues and attention deficit by first grade. To investigate this hypothesis, the researcher plans to interview 250 pre-kindergarten, kindergarten, and first-grade teachers across the county

Research: Yes

Research that involves human subjects: Yes

Exempt Research

- Some studies may be exempt
  - Commonly accepted educational settings
  - Educational tests
  - **Retrospective studies if unidentifiable or publicly available**
  - Taste and food quality evaluation
  - Consumer studies
- Decision must be certified by an IRB (not the investigator)

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Institutional Review Board (IRB)

- Federally funded human subjects research needs review and approval of IRB
- Individuals with different backgrounds discuss and make judgments about the acceptability of projects, based on the Common Rule
- IRBs must have at least five members:
  - One scientist
  - One nonscientist
  - “One member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution”

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IRB Authority

- Approve research activities and protocols
- Require modification
- Disapprove all research activities covered by the Common Rule
- Responsible for
  - Conducting continuing review of research
  - Ensuring that proposed changes in approved research are not initiated without IRB review and approval

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Federalwide Assurance (FWA)

- Human Subjects Research Must Be Guided by a Statement of Principles
- Compliance with Laws, Regulations, Policies, and Guidelines
- Written Procedures
- Institutional Support for the IRB(s)
- Reliance on an External IRB
- Renewal or Update of the Assurance

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UCSF Human Research Protection Program (HRPP)

Biggest Problems for Researchers

- Adhering to the approved protocol
- Following any additional IRB instructions
  - FWA - Federalwide Assurance can be suspended
- Keeping accurate records
- Promptly reporting any unanticipated problems
- Primary responsibility still lies with the researchers

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The following are examples of human subjects research guidelines:

The Common Rule 0%

The Belmont Report 0%

The Nuremberg Code 0%

The Declaration of Helsinki 0%

Three Rs of Alternatives 0%

Ethical Issues

- Informed Consent
- Right to Withdraw
- Risk Without Benefit

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Informed consent

- Research subjects should be
  - Fully informed about experiments
  - Consent before they enroll
- Some subjects cannot give informed consent
  - Children
  - Adults with impaired decision making capacity
  - Some critically-ill patients
- If possible, assent is required

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Right to withdraw

- Research subjects should have the right to withdraw from experiments *at any time*
- In some cases they cannot
  - Mechanical hearts
  - Vaccines
  - Gene therapy

- Right to withdraw from other aspects of study

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Risk without benefit

- Nuremberg Code- “[t]he degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”
- Common Rule - Risks must be reasonable in relation to the benefits
  - To the subjects
  - To the knowledge that may be gained

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HHS Proposed Major Revision to Common Rule

- Informed consent is “almost always” required for secondary use of biospecimens, *regardless of identifiability* – **not adopted** as final rule but may change in future.
- A single institutional review board review is mandated for multi-site research conducted at U.S. institutions.

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Biological Specimens

- Henrietta Lacks (HeLa) tumor cells
- Havasupai tribe diabetes study blood samples
- Newborns blood spots from standard metabolic screens

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Still No Need for IRB, but Continuous Review

- Maintain the status quo distinction between identifiable and nonidentifiable biospecimens
- **Research with nonidentifiable biospecimens will still not count as human subjects research** — and can be done without IRB
- However, within one year and every four years, regulators will reassess the definition of identifiable

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Big Data – Social Networks

Facebook PNAS 2015

Koko

A mental health tech company ran an AI experiment on real users. Nothing's stopping apps from conducting more.

NBC news

What ethical issue is most on your mind with regards to human subjects and AI?

Nobody has responded yet.

Hang tight! Responses are coming in.

Human Subjects - Clinical Trials

- FDA oversee clinical trials
- Early trials (phase 1) evaluate safety and treatment side effects
- Later trials (phase 2 and 3)
  - Evaluate how effective treatments are
  - Compare new therapies to standard treatments
- Sometimes trial phases are combined to expedite testing a treatment

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COVID-19 Vaccine Research (Moderna)

- Prior to COVID-19 pandemic average time to market for a vaccine was 10 years
- **With COVID-19, vaccines went into trials as quickly as 2 months after sequence of virus was known**
- mRNA technology is new and faster, allowing rapid development
- Governments, companies, research institutions pooled data and resources
- Clinical trial phases were overlapped to “hedge bets” and move quickly
- Recruitment for participants prioritized individuals with **high risk of infection**
  - Unavoidable exposure
  - Pre-existing conditions
- Phase 3 included 30,000 individuals, half received a placebo of saline

https://www.clinicaltrials.gov/ct2/show/NCT04470427

What ethical considerations occur to you given this trial design? Moderna COVID-19 Phase 3 Clinical Trial Design Inclusion Criteria: Participants who are at high risk of SARS-CoV-2 infection

Nobody has responded yet.

Hang tight! Responses are coming in.

CRISPR

- Current clinical trials blood disorders, cancers, inherited eye disease, diabetes, infectious disease, inflammatory disease, and protein-folding disorders
- All current trials are non-germline
- Example: Sickle Cell Disease
  - Ex-vivo gene editing reduces possible side effects from systemic exposure to editing tools
  - CRISPR/Vertex designed a single group open label study (no-placebo)

https://beta.clinicaltrials.gov/study/NCT03745287?patient=CRISPR%2FVertex&locStr=&distance=0
https://innovativegenomics.org/news/crispr-clinical-trials-2022/

Using CRISPR in humans: Under what circumstances should we use CRISPR in humans?

Nobody has responded yet.

Hang tight! Responses are coming in.

The Welfare of Laboratory Animals

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Animal research

- Conducted primarily for the benefit of humans
- We need to acknowledge the ethical dilemmas:
  - Animals cannot consent to participate
  - Animals cannot comment on their treatment
- Lack of agency places moral responsibility on researchers

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Federal regulations

- 1966 Animal Welfare Act (revised 1970, 1976, 1985, and 1990)
  - Assigns authority for the responsible transportation, care, and use of animals to the United States Department of Agriculture (**USDA**)
  - Covers animals used in research facilities, exhibition purposes, or for use as pets.
- 1985 Health Research Extension Act, Sec. 495
  - Delegates authority for the use of animals in "biomedical and behavioral research" to the Secretary of Health and Human Services (**HHS**), acting through the **NIH and OLAW**

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USDA and HHS

- Researchers who use animals in research, including observational research, or teaching, can come under either/both jurisdictions
  - USDA animal welfare regulations and/or
  - HHS Policy on Humane Care and Use of Laboratory Animals
- Researchers therefore should be familiar with both

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Guidelines

- 1950's- the "Animal Care Panel" (ACP) established a professional standard for laboratory animal care and facilities
- 1963- Guide for Laboratory Animal Facilities and Care
- Provides Guidance on:
  - Institutional Policies and Responsibilities
  - Animal Environment
  - Housing Management
  - Veterinary Medical Care
  - Physical Plant

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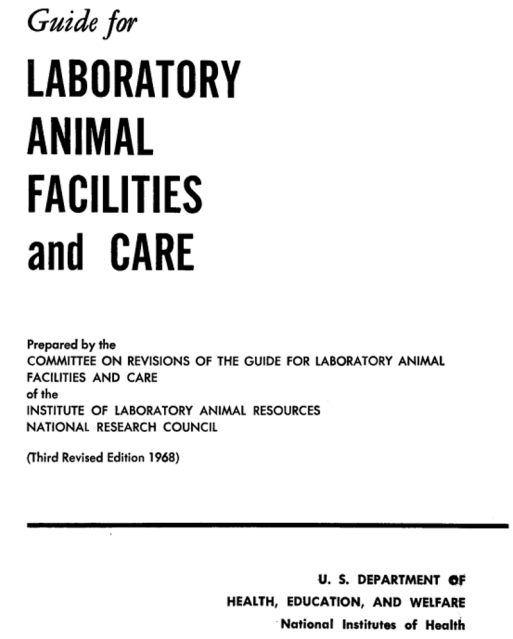
“The Guide”

The Guide is widely accepted by both government and research institutions as the most authoritative source of information on most animal care and use questions…



Guide for

LABORATORY ANIMAL FACILITIES and CARE

Prepared by the
COMMITTEE ON REVISIONS OF THE GUIDE FOR LABORATORY ANIMAL FACILITIES AND CARE
of the
INSTITUTE OF LABORATORY ANIMAL RESOURCES
NATIONAL RESEARCH COUNCIL

(Third Revised Edition 1968)

U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
National Institutes of Health

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IACUCs

- Research institutions must establish an IACUC
- IACUCs oversee and evaluate all aspects of the institution's animal program, procedures, and facilities.
- Must have at least 5 members:
  - A doctor of veterinary medicine
  - One researcher who uses animals in research
  - One person who is not affiliated with the institution
  - Many IACUCs also have a researcher who does not use animals and/or a member who has some grounding in ethics

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IACUCs responsibilities

- Reviewing and approving all animal proposals
- Reviewing the institution's animal care program
- Inspecting (at least twice a year) the institution's animal facilities
- Receiving and reviewing concerns
- IACUCs also have independent authority to suspend projects
- This authority comes directly from Congress

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Federal and Voluntary Oversight

- OLAW (NIH)
- USDA
- **Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)**

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OLAW

- Relies on an “Assurance” mechanism to monitor compliance
- A signed agreement submitted by a research institution
  - Comply with applicable rules and policies for animal care and use
  - Provide a description of the institution’s program for animal care and use
  - Maintain an appropriate IACUC
  - Appoint a responsible IO for compliance

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USDA

- Inspection-based system carried out by USDA Veterinary Medical Officers
- Announced or unannounced visits to check compliance
- If violations are found, the institution is then subject to administrative fines and penalties

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Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)

- Private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs
- More than 950 companies, universities, hospitals, government agencies and other research institutions in 41 countries have earned accreditation

Three Rs of Alternatives: Russell and Burch (1959)

- Replacement
- Reduction
- Refinement

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Replacement

- Using non-animal models
  - Microorganisms
  - Cell culture techniques
  - Computer simulations
  - Species lower on the phylogenetic scale

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Reduction

- Using methods aimed at reducing the numbers of animals
  - Minimization of variability
  - Appropriate selection of animal model
  - Minimization of animal loss
  - Careful experimental design

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Refinement

- The elimination or reduction of unnecessary pain and distress

The following are examples of voluntary oversight for animal research:

OLAW 0%

AAALAC 0%

The Three Rs of Alternatives 0%

USDA 0%

“The Guide” 0%

Ethical Issues

- Pain and suffering
- Concern for different species
- Unnecessary experiments

Pain and suffering

- Some information cannot be gained without pain and suffering
- Researchers studying trauma
  - Administering electric shock
  - Forcing animals such as rats to swim until they reach exhaustion
- How much pain and suffering is acceptable in experiments is not easily determined

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Unnecessary experiments

- Animal research remains controversial
- Animals are used to test the safety of experimental drugs should they also be used to test the toxicity of chemicals or cosmetics?
- Do researchers sometimes use more animals in an experiment than is absolutely necessary?
- Do researchers use animals when other means of testing would provide the same information?

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End for today

Collaboration

What constitutes collaboration?

- Sharing reagents, techniques, info or samples
- Small joint project
- Multi-center projects
- Not necessarily geographically close locations
- Potentially competing interests

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Effective collaboration begins with…

"A clear understanding of roles and relationships, which should begin the day the collaboration is established by discussing the details of the collaboration."

Office of Sponsored Research

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Details to know…

- Goals of project & anticipated outcomes
- Role of each partner in collaboration
- How data will be collected, stored & shared
- How design changes will be made
- Publication responsibilities
- Criteria for authorship
- Conflicts of interest

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Details to know…(2)

- Who will submit reports & meet requirements
- Who can/will speak publicly about this work
- Intellectual property rights & ownership
- Changes to agreement & when it comes to an end
- Ownership of spin-off projects
- Check-points & kill-points
- Fate of samples/materials at end of project

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Communication plans

- Establish schedule of regular meetings/visits
  - Report findings, preliminary results
  - Discuss the changing landscape of the project
  - Discuss recent developments in the field
- Establish regular discussion of financial issues
  - Particularly important if project is funded
  - Report run-of-the-mill expenses & anticipated spending

Informal Agreements

- Unfunded
- Charter and/or Meeting Minutes
  - Shared drive document
  - Email
- Updates after meetings or new results

Invention disclosure:
What do I do when I have made a discovery?

"Employees of the University have an obligation to disclose their inventions in writing to the Office of Technology Licensing (OTL) … if a disclosure is made to the OTL after it has been publicly disseminated in an enabling way … patent rights outside of the United States are generally not available…

The optimal time to disclose is after the invention has been conceived and initial data are available, but before it has been publicly divulged."

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https://techtransfer.universityofcalifornia.edu/IPAwareness/story_html5.html

UCSF Innovation Ventures

https://innovation.ucsf.edu/

End for today