

Why should we care about protecting human research participants and how can we do it well?

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Disclaimer

The opinions expressed are those of the presenter and do not necessarily reflect the policy of the U.S. Department of Health and Human Services.



Learning Objectives

- Explain the ethical tension with advancing science through human subjects research
- Discuss the regulatory framework for protecting research participants in the U.S.
- Describe the considerations that need to be explored to protect participants of research



Human Research: An Inherent Ethical Tension

- Research is about promoting the common good
- Research subjects are the means to achieve this goal
 - In the pursuit of the common good, it is not always easy to manage competing interests and the rights and welfare of individual research subjects could easily be overlooked



The Syphilis Study in Tuskegee, Alabama



- Began as an initiative to document the natural history of syphilis
- Researchers only told subjects that they were being treated for “bad blood,” did not tell them about the study, did not obtain consent
- When penicillin became available as an effective treatment, subjects:
 - Were not informed of its availability
 - Were not given the treatment
 - Were even prevented from finding out and accessing the treatment

The Tearoom Trade Study

- A social science study examining a phenomenon in the 1960's
- While the work was recognized as valuable, the methodology used provoked controversies and public outcry
- Researcher used deceptive methods to gain people's trust, conducted the study without appropriate informed consent, invaded people's privacy and potentially put them at risk of harm



Regulations Developed on Ethical Principles

Principles of the Belmont Report

Regulatory Requirements

Respect for Persons

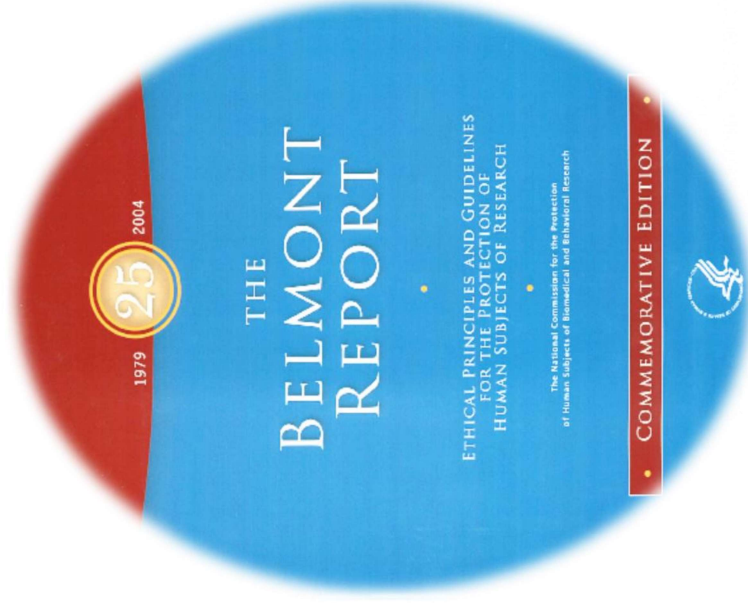
- Informed Consent (information, comprehension, & voluntariness)
- Provide information a reasonable person would want to make decision about participation

Beneficence

- Minimize risk of harm
- Favorable risk/benefit assessment

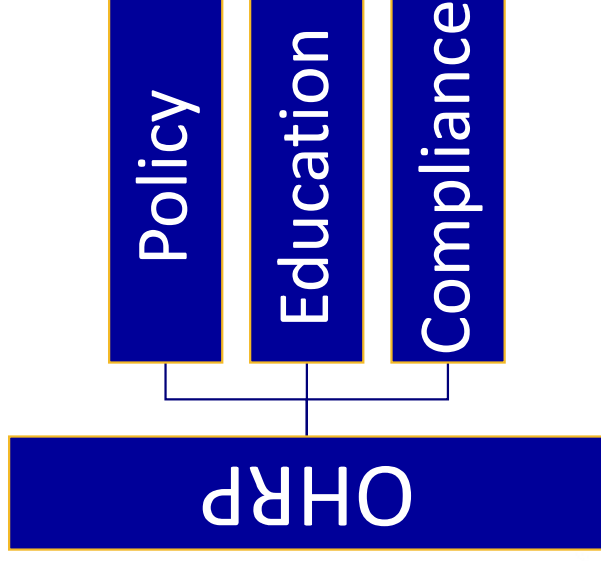
Justice

- Select individuals/groups of subjects equitably
- Link burdens to benefits



The Office for Human Research Protections (OHRP)

OHRP holds the regulatory authority for 45 CFR 46 and provides leadership in protecting human subjects in research conducted or supported by HHS



The HHS Regulations for Human Research Protections

45 CFR part 46

- **Subpart A – The Common Rule**
- Subpart B – Pregnant women & fetuses
- Subpart C – Prisoners
- Subpart D – Children
- Subpart E – IRB Registration

CR Departments & Agencies



How Does the Common Rule Work?

Regulatory requirements for protections apply to:

- **Nonexempt human subjects** research that is **funded by HHS** (or other Common Rule agencies and departments)
- Institutions can also use the Common Rule framework for research oversight with their own institutional policies regardless of funding

Note: The regulatory framework provides a baseline standard for human research protections. Mere compliance does NOT mean that the research study is necessarily protective or free from ethical concerns!



When Do the Common Rule Requirements **Not** Apply and What Does That Mean?

Regulatory requirements do not apply:

- When project is **not** *Research*, or
- When project is **not** *Human Subjects Research*, or
- When project is ***Exempt Human Subjects Research***



Investigators/Institutions have **Flexibility** outside the regulations

(Should still pay attention to participants' rights & welfare)



What is Research?

Research refers to a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (§46.102(I)).

Not Research Examples:

- Biographies
- Employee satisfaction surveys
- Case studies



Are QI/QA Activities Research?

The Common Rule does not define QI/QA

- The Common Rule applies to QI/QA activities if they are **non-exempt, human subjects research**
- Often, the question is whether QI/QA activities meet the regulatory definitions of **research**
- So, for QI/QA activities, always ask the question: is it a **systematic investigation** designed to contribute to **generalizable knowledge**?



Categories of Activities Specifically Deemed “Not Research” (1)

Scholarly and journalistic activities

- Focus on the specific individual about whom information is collected
- Excludes certain activities, not entire academic fields

§46.102(I)

Example: Oral history interviews with survivors of 9/11.



Categories of Activities Specifically Deemed “Not Research” (2)

Government functions with separately mandated protections

- Public health surveillance activities

§46.102(l)

Example: Reporting on newly observed phenomena related to COVID infection.

This is NOT research if the activities come under the Public Health Surveillance exclusion.



What is Human Subjects Research?

Human subject - a living individual about whom an investigator conducting research

(i) Obtains **information or biospecimens** through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens;

or

(ii) Obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**



§46.102(e)(1)(i)

What Does *Identifiable* Mean Under the Common Rule?

Definition for “Identifiable”:

Identifiable private information or identifiable biospecimens refers to private information or biospecimens ***for which the identity of the subject is or may readily be ascertained by the investigator or associated with the*** information or biospecimens

- The Common Rule does not define other associated terms, such as, *coded, de-identified, or anonymized*
- It does not have a list like the “HIPAA identifiers”
- Unique identifiers may not necessarily be “identifiable” under the Common Rule



When is Research Not Human Subject Research?

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

- x** 1) Obtains information or biospecimens **through intervention or interaction** with the individual, and uses, studies, or analyzes the information or biospecimens; **or**
- x** 2) Obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**

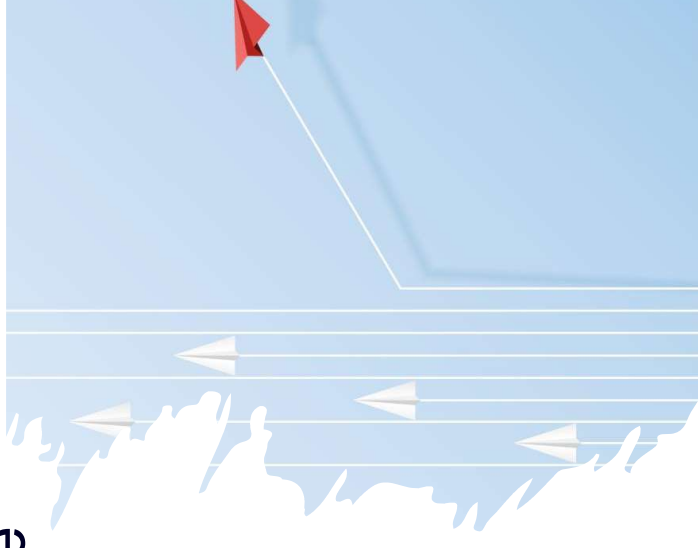
§46.102(e)(1)



Exempt Research

What does it mean for a research project to be exempt?

- It is human subjects research
- It meets the criteria of one of the exemptions listed in §46.104
- If determined to be exempt:
 - Generally, no requirement for IRB review
 - Some exemptions require a **limited IRB review** as part of the exemption determination
 - Generally, no requirement for obtaining and documenting informed consent
 - Some exemptions require Broad Consent



Summary of the Eight Exempt Categories

Exemption 1: Normal educational practices in established educational settings

Exemption 2: Educational tests, surveys, interviews, or observation of public behavior

Exemption 3: Benign behavioral interventions

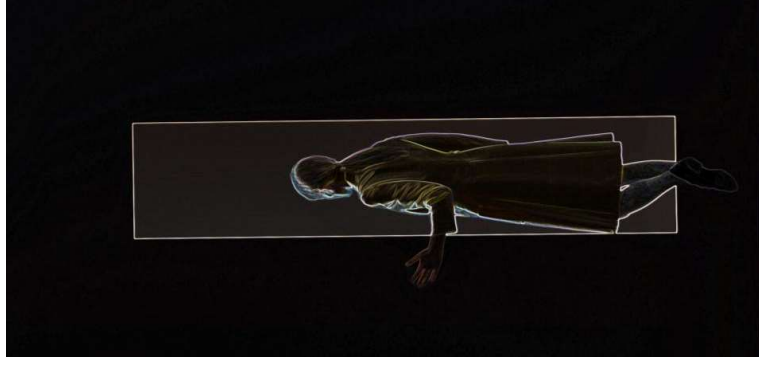
Exemption 4: Secondary research use of identifiable biospecimens or information for which informed consent is not required

Exemption 5: Evaluation of public benefit and service programs

Exemption 6: Taste and food quality evaluation & customer acceptance studies

Exemption 7: Storage and maintenance of identifiable materials for unspecified secondary research with broad consent

Exemption 8: Secondary research use of identifiable materials with broad consent



What Does It Mean When the Common Rule Requirements **Apply**?

- Regulatory requirements apply when research is ***nonexempt human subjects research***
- This means (among others):
 - Requirement for review and approval of research, according to a set of regulatory criteria, by an Institutional Review Board (IRB) with a defined membership and setup
 - Requirement to obtain informed consent as stipulated by the regulations unless waived



Criteria for IRB Review and Approval of Research at §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 knowledge that may reasonably be expected to result

Selection of subjects is equitable

Informed consent will be obtained and documented (unless waived) accordingly

There are adequate provisions for data monitoring to ensure safety of subjects if appropriate

There are adequate provisions to protect the privacy of subjects and to maintain confidentiality of the data if appropriate

There are additional safeguards to protect the rights and welfare of subjects likely to be vulnerable to coercion or undue influence

Criterion: Equitable Selection of Subjects

Consider:

- a) Is the hypothesis clear? Is it clearly stated? Is the research design appropriate for answering the question?
- b) Who is the target population? Is the target population appropriate for answering the questions the protocol addresses?
- c) Is the inclusion criteria adequately inclusive so that the distribution of potential benefits is fair?
- d) Are investigators excluding certain population groups without valid justifications?



Criterion: Risks to Subjects are Minimized

Consider:

- a) Is the study design appropriate (e.g., are the research procedures necessary) for proving the hypothesis?
- b) What are the risks of the research? Consider the **likelihood** and the **magnitude**
- c) Does the research design include measures to minimize risks to subjects?

For example,

- 1) Piggy-backing on procedures that would be done regardless of the research;
- 2) Incorporating measures that would minimize subjects' risk exposure

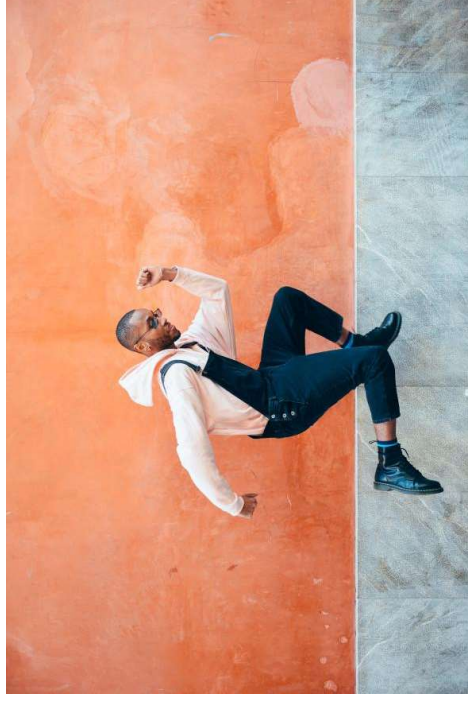


Criterion: Risks to Subjects are Reasonable in Relationship to Anticipated Benefits

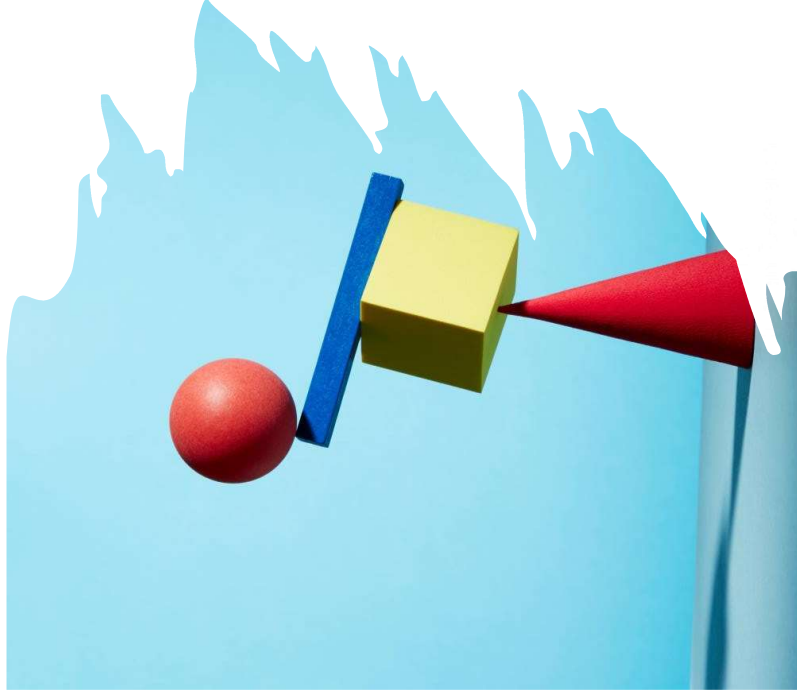
What benefits and for whom?

Consider:

- a) What are the risks that may result from the research?
- b) What is the prospect of direct benefit that may result from the research and what this might mean?
- c) Are the risks reasonable to the benefits taking into consideration the importance of the knowledge that could be gained



Criterion: Additional Safeguards for Vulnerable Subjects



Subjects **vulnerable to coercion or undue influence**, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons...

Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance

Undue influence occurs through an offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance

Criterion: Informed Consent Obtained/Documented

- Must be obtained and documented **before** beginning any activities done for research purposes (unless waived)
- Informed consent must provide information:
 - **Needed** for an informed decision about participation
 - In language **understandable** to the potential participant
 - Under circumstances that promote **voluntariness**



*This is not how you would get consent!

Additional Informed Consent Requirements in the 2018 Common Rule

Focus on the information needs of prospective research participants, including:

- Information that **a reasonable person** would want to have in order to make an **informed decision about participation**
- Information presented in **sufficient detail and organized and presented in a way that facilitates understanding of why one might or might not want to participate**

46.116(a)(4) & §46.116(a)(5)(ii)



Significance of Informed Consent

- Research collects data to answer questions that would promote the common good. Research subjects are the means to achieve this goal
- Through the informed consent process, individuals make autonomous, informed decisions about their participation in research
- Informed consent renders research ethical so that the public can continue to have trust in the research enterprise



Case Study – Interviews and Surveys

- Treating oncologists want to assess the psychological, physical, social, and emotional aspects of cancer diagnosis in adolescent patients.
- Patient prognosis is less than 12 months to live.
- Patients will partake in a single 90-to-120-minute interview with their physician/researcher in clinic or at home.
- Patients will complete a series of surveys over a 6-month period on suicidality, alcohol and drug use and dependence, mental health, quality of life, anxiety, etc.
- Researchers will also conduct virtual focus groups with family members.



Case Study - Some Review Considerations

- Who are the research subjects here? anticipated benefits?
- What's the appropriate review criteria?
 - Will informed consent be obtained and documented?
- Do the other Subparts apply?
 - Are there adequate provisions to protect privacy of subjects? To maintain confidentiality of the data?
- What are the risks to subjects and have they been minimized?
 - Are any of the subjects vulnerable to coercion or undue influence?
- What are the anticipated benefits?
 - Are there additional safeguards to protect the rights and welfare of vulnerable subjects?
- Are risks to subjects reasonable in relation to

OHRP PUBLIC OUTREACH RESOURCES

www.hhs.gov/About-Research-Participation

Educate prospective participants!
Resources also in Spanish!

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Informational Videos

Human Research Volunteer Informational Videos

View in [English](#) | Ver en [Español](#)

Glossary of Terms in [English](#)

These short videos provide basic information about human research, including clinical trials, medical research, and other kinds of research. They help potential research volunteers understand how research works, what questions they should ask, and things to think about when deciding whether to participate in a study.

Videos on Clinical Research Basics



Part 1: What is Medical Research?



Part 2: Deciding to Participate in Clinical Trials



Part 3: Questions to Ask Researchers in Clinical Trials



Explaining Researcher's Role in Clinical Trials



Understanding the Differences



How is Medical Research Different from Medical Care?

Videos on Other Types of Human Research



Research with Medical Records and Samples



Participating in Social and Behavioral Health Research

QUESTIONS TO ASK

when deciding whether to volunteer for research

About the Research

1. What is the researcher doing and why is it being done?

2. What are the risks and benefits of the study?

3. What are the risks and benefits of the study?

4. What are the risks and benefits of the study?

5. What are the risks and benefits of the study?

6. What are the risks and benefits of the study?

7. What are the risks and benefits of the study?

8. What are the risks and benefits of the study?

9. What are the risks and benefits of the study?

10. What are the risks and benefits of the study?

Risks Involved

11. How much time will you have to spend on the study?

12. How much time will you have to spend on the study?

13. How much time will you have to spend on the study?

14. How much time will you have to spend on the study?

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20. How much time will you have to spend on the study?

Privacy and Confidentiality

21. How much time will you have to spend on the study?

22. How much time will you have to spend on the study?

23. How much time will you have to spend on the study?

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28. How much time will you have to spend on the study?

29. How much time will you have to spend on the study?

30. How much time will you have to spend on the study?

Financial Considerations

31. How much time will you have to spend on the study?

32. How much time will you have to spend on the study?

33. How much time will you have to spend on the study?

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40. How much time will you have to spend on the study?

Additional Considerations

41. How much time will you have to spend on the study?

42. How much time will you have to spend on the study?

43. How much time will you have to spend on the study?

44. How much time will you have to spend on the study?

45. How much time will you have to spend on the study?

46. How much time will you have to spend on the study?

47. How much time will you have to spend on the study?

48. How much time will you have to spend on the study?

49. How much time will you have to spend on the study?

50. How much time will you have to spend on the study?

Questions to Ask

Questions to Ask About Volunteering for a Research Study

These questions will help you get the information you need to decide whether to volunteer to participate in a research study.

View in [English](#) | Ver en [Español](#)

[Glossary of Terms in English](#)

[More Resources](#)

[Print this List of Questions](#)

ABOUT THE RESEARCH

Ask about what you would do in the study and how participating might affect you.

WHAT WOULD HAPPEN

Ask about what you would do in the study and how participating might affect you.

RISKS INVOLVED

Ask about potential risks and what researchers will do to minimize them.

PRIVACY & CONFIDENTIALITY

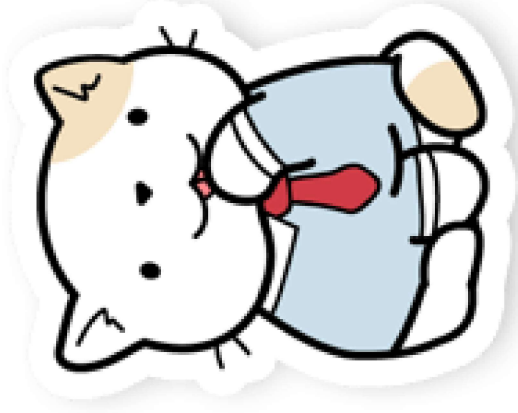
Ask how your privacy and your personal information will be protected.

FINANCIAL CONSIDERATIONS

Find out if there are costs and who would pay for them.

Contacts and Resources

- Contact us or submit your questions to OHRP@hhs.gov
- Visit OHRP website at www.hhs.gov/ohrp
- Visit OHRP's [DED page!](#)



Thank you!

Questions?

