Unlocking the Mysteries of the §46.111 Criteria for IRB Approval of Research

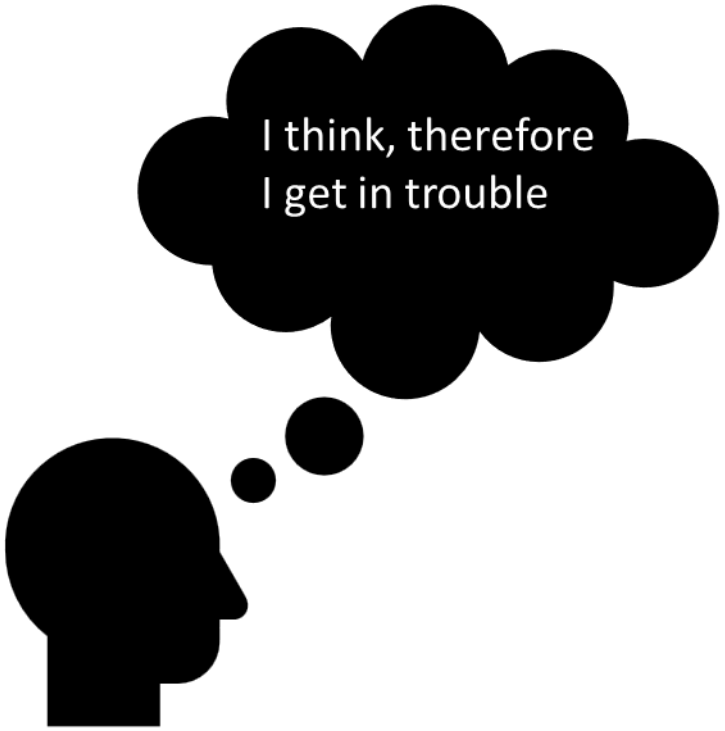
July 11, 2023

OASH | Office for Human Research Protections

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.

For a complete and accurate description of the regulatory requirements, please refer to the text of the revised Common Rule available on OHRP's website.



Learning Objectives

- Examine the criteria for Institutional Review Board (IRB) review and approval of research at §45 CFR 46.111
- Consider what IRBs look for when reviewing research under §46.111
- Apply the §46.111 criteria to case studies

When Do the Regulatory Requirements at §45 CFR 46 Apply and What Does That Typically Mean?

- **Apply to non-exempt human subjects research** that is **funded or conducted by HHS** (or other Common Rule agencies and departments)
- Among other things, this includes requirements for, for example:
  - Review and approval of research, according to a set of regulatory criteria, by an IRB with a defined membership
  - Requirement to obtain informed consent as stipulated by the regulations unless waived

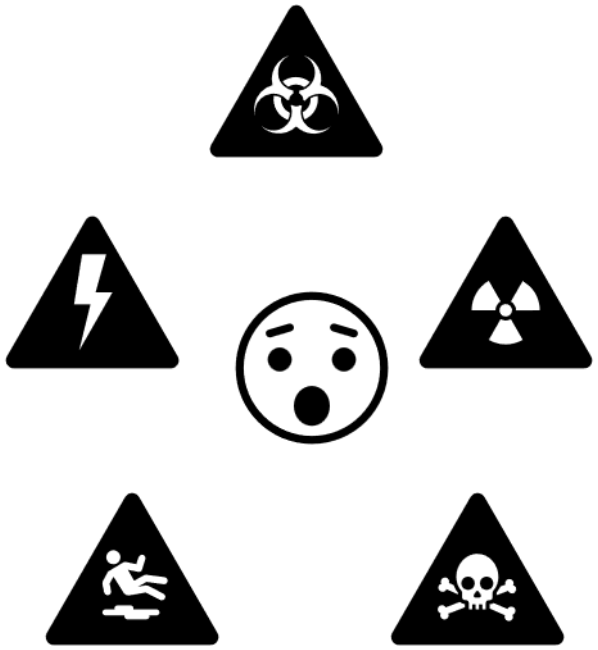
Criteria for IRB Review and Approval of Research at §46.111 (excluding limited review)

- 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

Review Criterion – Risks to Subjects Are Minimized

"**Risks to subjects are minimized**: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes."

§45 CFR 46.111(a)(1)



The Concept of Risk

The *possibility* that something unpleasant or unwelcome will happen

- Generally, not objectively quantifiable
- Inherently imprecise
- Perception perspective – subjective and value-dependent

Regulatory Definition: "Minimal Risk"

"Minimal risk means that 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."

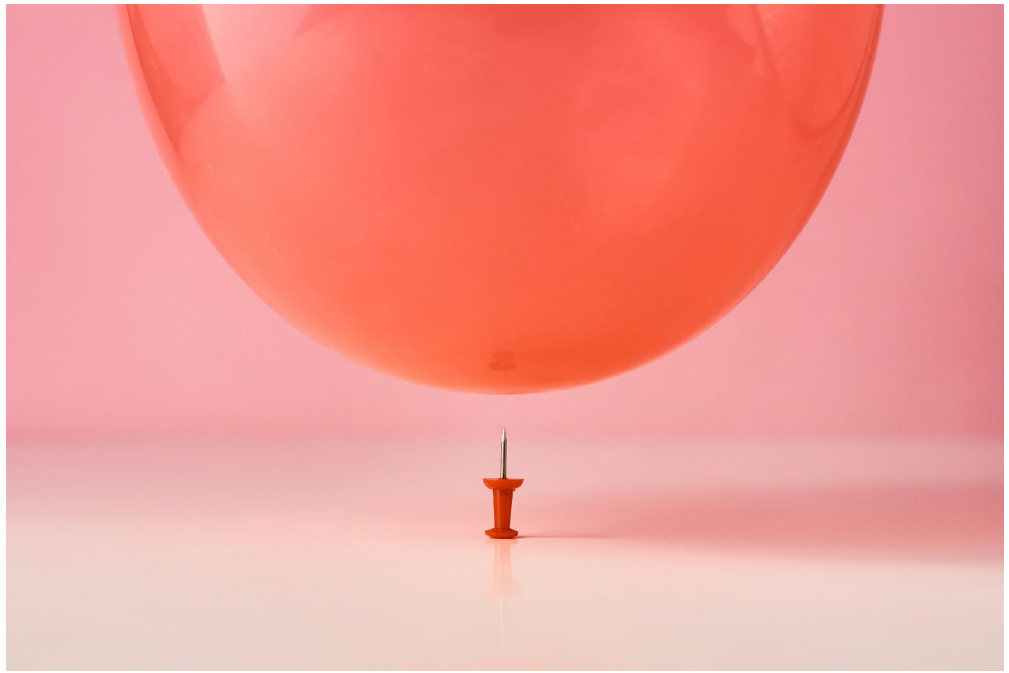
- Risk is a function of:
  1) **Magnitude** (how severe), and 2) **Probability** (how likely)

- Research risks are compared to three standards of reference:
  - Daily life
  - Routine physical examinations or tests
  - Routine psychological examinations or tests

§45 CRF 46.102(i) (emphasis added)

Risks – What to Consider?

- Is the hypothesis clear?
- Is the study design appropriate to prove the hypothesis?
- Is the research designed with appropriate measures to minimize risks to participants?
- Is there appropriate use of the exclusion criteria? Do the criteria serve to minimize risks?



Think Critically About Risks

Type of Risk

- Physical
- Psychological
- Social
- Economic
- Legal
- Dignity/respect

Circumstances for Risk

- Recruitment
- Giving informed consent
- Performing a research activity
- Identifiability of Responses

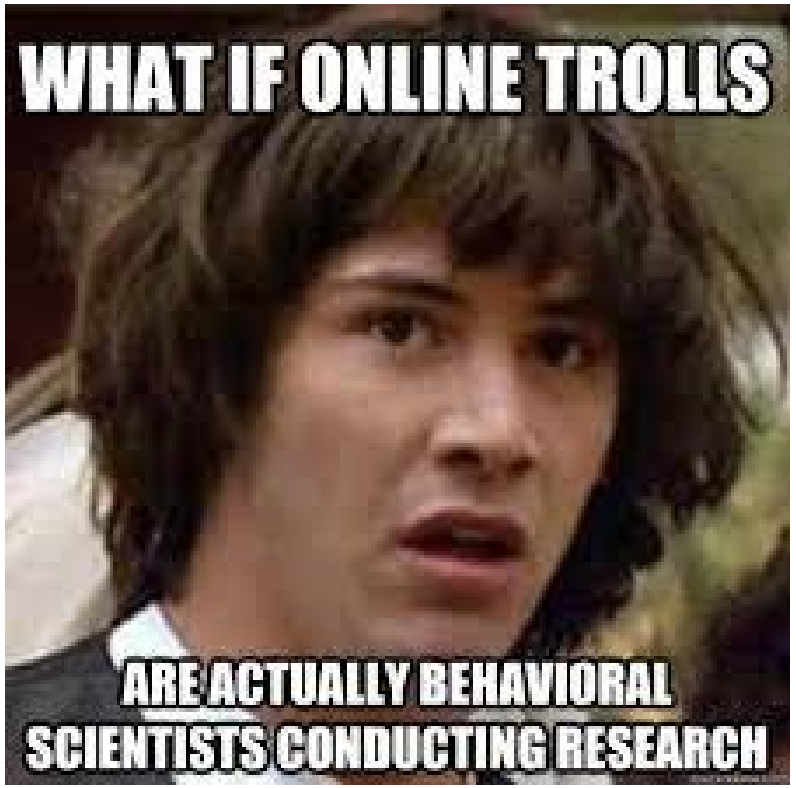
(Names may not be needed to identify)

Who Is Impacted

- Research Subjects
- Others

(Not explicit in regulations but a consideration within broad concept of beneficence)

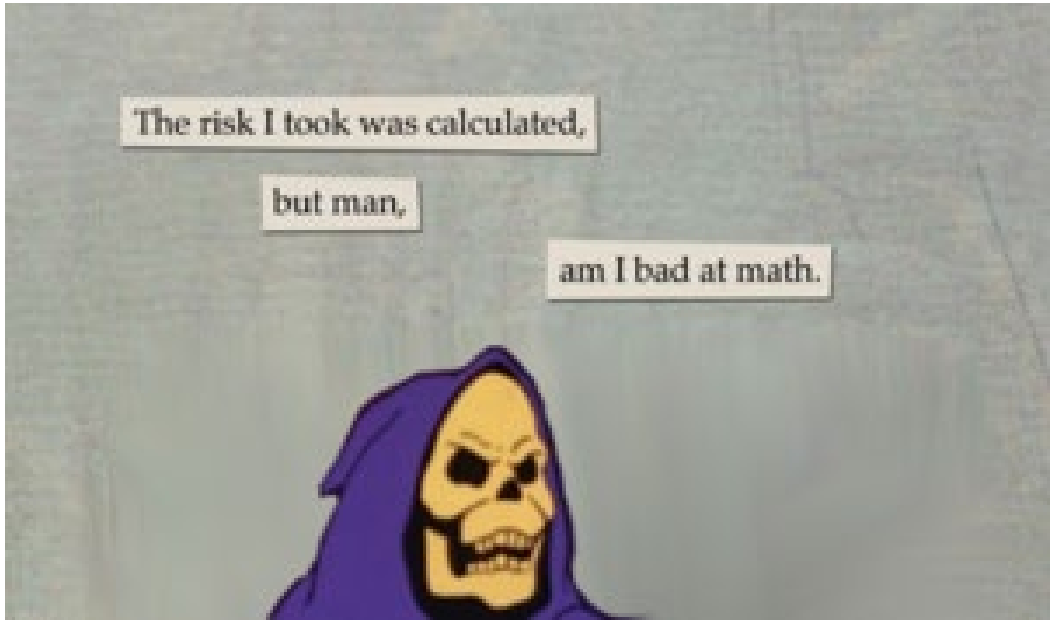
Identifying Risks: Additional Considerations for Social and Behavioral Research



- Risks may often be less obvious and more difficult to identify
- Risks can be both time- and situation-specific
- Risks can be subjective; relevant to the specific populations, or even individuals, involved
- Requires considering the specific features of a study; context matters
- Lack of empirical data may complicate risk assessment

Minimizing Risk – What to Consider?

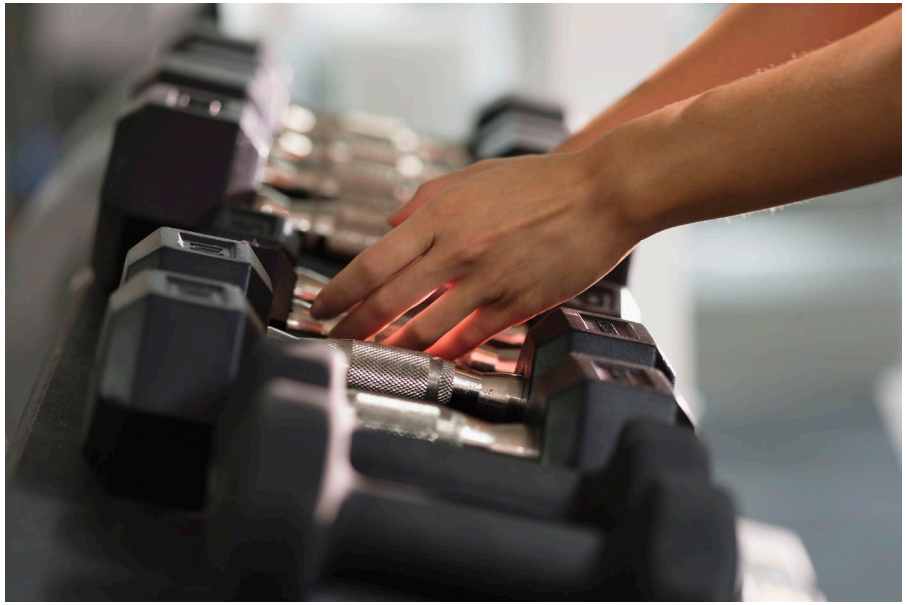
- Alternative procedures/methods that are less risky
- Precautions that decrease the likelihood of harms occurring
- Contingency procedures to address harms if they do occur
- Piggyback on clinical care procedures that will be done regardless of the research



Case Study 1

Researchers plan to collect data from 200 adults to map the physiological changes in the body due to exercise. Study aims to measure physiological changes before, during, and after exercise.

Sedentary adults will be assigned to an endurance training regimen (treadmill, cycling) or a resistance training regimen (weightlifting).



Quiz 1 – What are some ways in which the risk of exercise-related injuries in this study could be minimized? (select all that apply)

- ✓ ☑Study team must include certified fitness trainers with experience teaching exercises to sedentary people
- ✓ ☑Participants must wear proper attire, including shoes, for the exercise activities
- ❑ A television should be within viewing distance of participants during exercise activities
- ✓ ☑Participants must warm up before exercise to avoid injury

Review Criterion – Risks to Subjects Are Reasonable in Relation to Anticipated Benefits

"**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..."

§45 CFR 46.111(a)(2)

What Questions Should We Ask?

a) What are the risks that may result from the research? Consider the likelihood and the magnitude.

b) What is the prospect of direct benefit that may result from the research and what might this mean?

c) What is the knowledge that may be gained?

d) Are the risks reasonable to the benefits taking into consideration the importance of the knowledge that could be gained?

Weighing risks against benefits:

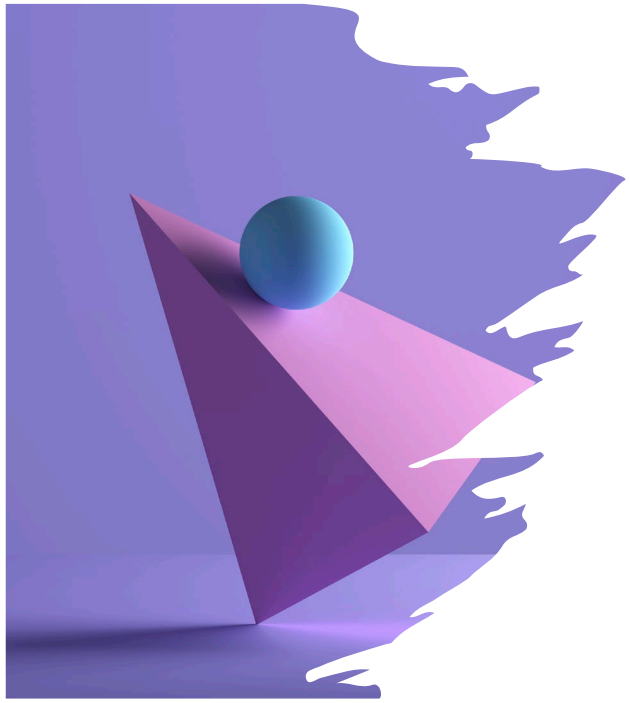
Identifying risks

Forecasting benefits

- Benefits to subjects
  - ✓Direct or indirect
- Benefits to others
  - ✓Importance of knowledge, significance of benefits

Tip: Develop and follow a framework to reduce subjectivity

Risk/Benefit Analyses – No Formula, Only General Concepts



- No direct benefit: serious risks may be justified only if knowledge to be gained is important and cannot be obtained otherwise
- Direct benefit: reasonable amount of risk may be justifiable
- Studying a new treatment: generally no more risk than available treatments, unless justified by potential benefits
- Consider if placebo should be used when accepted therapy exists

Case Study 2

Researchers are conducting a study to examine prevalence of migraines in African American men ages 18-55.

Participants will complete a series of questionnaires on physical and mental health, medical history, family history, and social relationships, provide a blood sample for testing, and undergo a lumbar puncture.

Research risks include breach of privacy and confidentiality, bruising from blood draw, side effects from lumbar puncture, and distress associated with completing the research questionnaires. Research benefits include contributions to generalizable knowledge and scientific progress.

Quiz 2 – Are risks to subjects reasonable in relation to anticipated benefits?

- ❑ Probably Yes
- ✓ ☑Probably Not
- ❑ It Depends

Review Criterion – Selection of Subjects Is Equitable

Things to consider:

a) Who is the target population?
b) Is the target population appropriate for answering the questions the protocol addresses?
c) Is the inclusion criteria sufficiently inclusive?
d) Are the reasons for exclusion scientifically valid?
e) Are there adequate additional safeguards for potentially vulnerable subjects?

§45 CFR 46.111(a)(3)

Equitable Selection and Reasonable Risks-Benefits Consideration

A fair distribution of the burdens and benefits of research requires an understanding of:

a) What are the benefits and for whom?

- What steps could be taken to maximize benefits, including a bigger reach?

b) What are the burdens and on whom?

- Burdens may not just be the risk of research. They may include time, effort, cost, and other less tangible burdens.
- What measures could be taken to lessen the burdens?

§46.111(a)(2) and (3)

Review Criteria – Informed Consent Will be Obtained and Documented

- Obtained and documented ***before*** beginning any activities done for research purposes (unless waived or altered, or procedure satisfies the "screening exception" at 46.116(g))
- Informed consent must provide information:
  - **Needed** for an informed decision about participation
  - In language **understandable** to the potential participant
  - Under circumstances that promote **voluntariness**

§46.111(a)(4) and (5)

Review Criterion – When Appropriate, Adequate Provisions for Data Monitoring to Ensure Safety of Subjects

Things to consider:

a) Is there a Data Safety Monitoring Plan (DSMP)? Data Safety Monitoring Board (DSMB)?

b) Is the monitoring plan appropriate and adequate?

§46.111(a)(6)

Review Criterion – Adequate Provisions to Protect Privacy and Maintain Confidentiality

Things to consider:

a) Will personally-identifiable research data be protected to the extent possible from unauthorized access or use?

b) Are any special privacy and confidentiality issues properly addressed, e.g., use of genetic information?

§46.111(a)(7)

Case Study 4

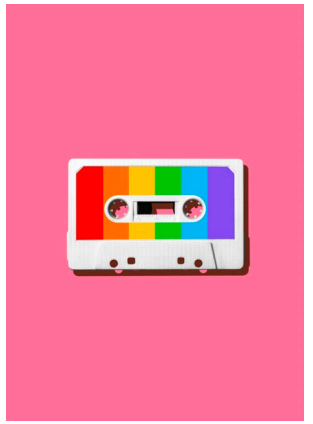
A study will qualitatively examine and describe the ways in which trans people experience sexuality and explore how trans individuals describe the connection between gender and sexuality.

Individual and focus group interviews will be conducted at the university faculty lounge.

Researchers will use personal cell phones to audio-record the individual and focus group interviews.

Quiz 4 – What are some study design changes that might better protect the privacy of participants and the confidentiality of their data? (select all that apply)

- ✓ ☑ Conduct individual and focus interviews in a private space
- ✓ ☑ Notify focus group participants not to discuss what is said by others
- ✓ ☑ Use a digital voice recorder to record the interviews
- ❑ Store all research data on a personal computer connected to public Wi-Fi



Additional Safeguards for Vulnerable Subjects

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

Things to consider:

- Are potentially vulnerable populations involved?
- What kind of vulnerabilities?
  - Are they intrinsic vulnerabilities, e.g., limitation in mental capacity because of age or illness?
  - Are the vulnerabilities by reason of extrinsic factors, e.g., socio-economic structures or other social determinants?
- Are the vulnerabilities amenable to measures that can reverse the situation or lessen their impact?

§46.111(b)

Additional Requirements for Reviewing Subpart Populations

45 CFR part 46

- Subpart A – The Common Rule
- **Subpart B – Pregnant women and fetuses**
- **Subpart C – Prisoners**
- **Subpart D – Children**

The Role of Researchers

- Learn the regulatory requirements and ethical principles
- Remember that research is a privilege and participants are not a means to research ends
- Respect, value, and know/understand research participants
- Submit clear, complete, and mutually-consistent research proposals and associated documents to the IRB for review
- Follow institution's submission guidelines and applicable institutional policies
- Allow sufficient time for review
- Collegially work with the IRB to respond to its questions and requests for changes
- Keep the IRB apprised of the research post-approval

Educational Resources Highlights

www.hhs.gov/ohrp/education-and-outreach/index.html

Or write to OHRP-EDU@hhs.gov for information

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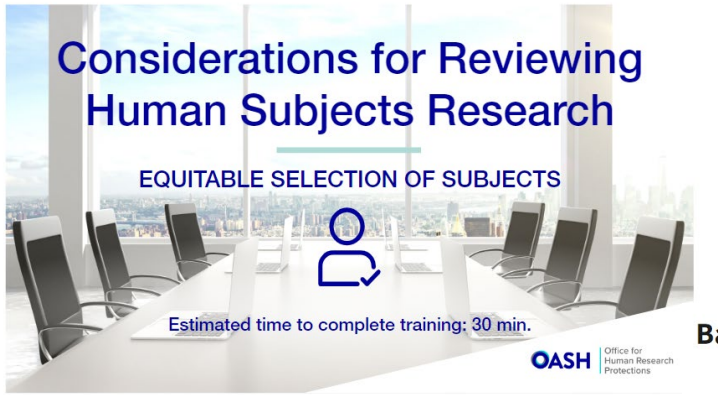
Considerations for Reviewing Human Subjects Research – Interactive Programs!

Equitable Selection of Subjects

Equitable Selection of Subjects



Minimizing Risks in Research

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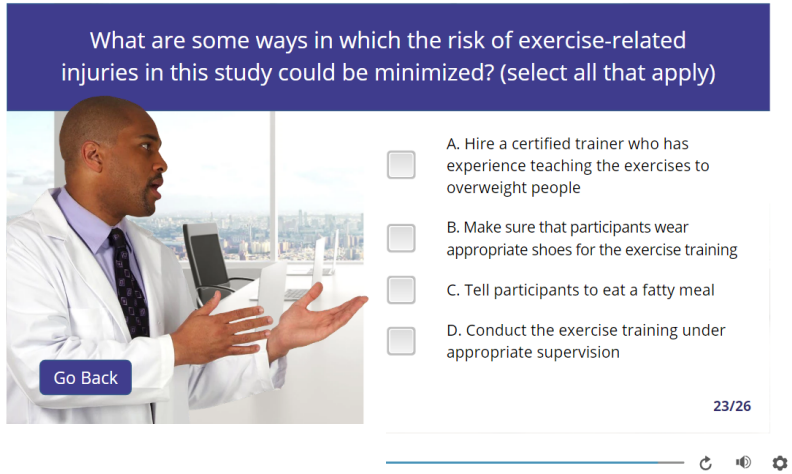

Balancing Risks and Benefits

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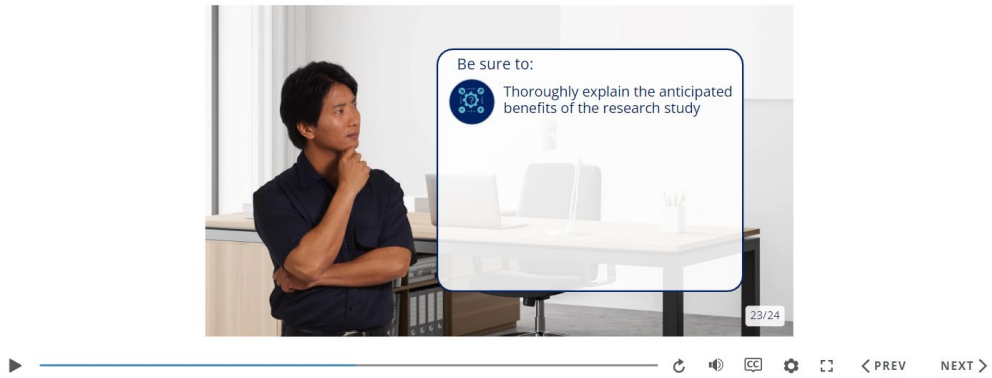

https://www.hhs.gov/ohrp/education-and-outreach/human-research-protection-training/considerations-for-reviewing-human-subjects-research/index.html

Upcoming OHRP Educational Events

www.hhs.gov/ohrp/education-and-outreach/index.html

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2023 OHRP Exploratory Workshop

Livestream on Thursday, September 14, 2023
9:45 AM – 4:20 PM EDT
No registration required

Psychedelics are powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes. Their origins predate written history, and early cultures used them in many sociocultural and ritual contexts. The name 'psychedelics' was coined by Humphrey Osmond in 1957, suggesting that they have a mind-manifesting capability that may reveal useful or beneficial properties of the mind. For decades, psychedelics have been classified as illegal drugs. Recent research suggests that these substances may provide a potential breakthrough in the treatment of a myriad of mental health conditions. This exploratory workshop will examine the ethical and practical considerations for psychedelics research with the goal of promoting an open and grounded discourse on how to conduct research that is inclusive and protective of participants.

Access workshop website from OHRP homepage or directly at:

https://www.hhs.gov/ohrp/education-and-outreach/exploratory-workshop/index.html

Save the date! OHRP's next Research Community Forum (RCF) will be held in beautiful Ann Arbor, Michigan on September 26-27

Making a difference in human subjects research: empowering participants, engaging communities, and protecting data

September 26 - 27, 2023
Ann Arbor, Michigan

https://research-compliance.umich.edu/human-subjects/ohrp-research-community-forum

Contacts and Resources

- Contact us or submit your questions to OHRP@hhs.gov
- Visit OHRP website at www.hhs.gov/ohrp
- Bookmark this page for quick reference to OHRP resources on the revised Common Rule: www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html
- Complete our Human Research Protection Training!
- Visit our website to view our Online Education content.


Thank you!