Part II - What Investigators Should Know About IRB Review

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Disclaimer

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Learning Objectives

- Discuss what IRBs look for when reviewing research
- Explain how to prepare a research proposal that addresses the regulatory requirements for review, including the requirements for informed consent
- Help investigators understand their responsibilities with respect to IRB review and protections of human research participants

What Does It Mean When the Regulatory Requirements Apply?

- **Apply to non-exempt human subjects** research that is **funded by HHS** (or other Common Rule agencies and departments)
- 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 (§46.111)

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of knowledge that may be reasonably be expected to result
- Selection of subjects is equitable. Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence
- Informed consent will be obtained and documented accordingly
- Adequate provision for data monitoring to ensure safety of subjects
- Adequate provisions to protect the privacy of subjects and to maintain confidentiality of the data
- Additional requirements for reviewing Subpart B, C, and D populations

Evaluation of Applications and Proposals for Research to be Conducted or Supported by a Federal Department or Agency (e.g., NIH) (§46.120)

Conditions for Review:

- Risks to the subjects
- Adequacy of protection against these risks,
- Potential benefits of the research to the subjects and others
- Importance of the knowledge gained or to be gained

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one

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)

Things to consider:

a) Is the hypothesis clear? Is it clearly stated?

b) Is the study design appropriate to prove the hypothesis?

c) Does the research design minimize risks to subjects?

d) Is there appropriate use of the exclusion criteria? Do the criteria serve to minimize risks?

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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." §45 CRF 46.102(i) (emphasis added)

- 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

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Think Critically About Risks

Type of Risk

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

Circumstances for Risk

- Recruitment
- Informed Consent
- Participation
- 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)

Minimizing Risk

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

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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..." (emphasis added) §45 CFR 46.111(a)(2)

Things to consider:

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

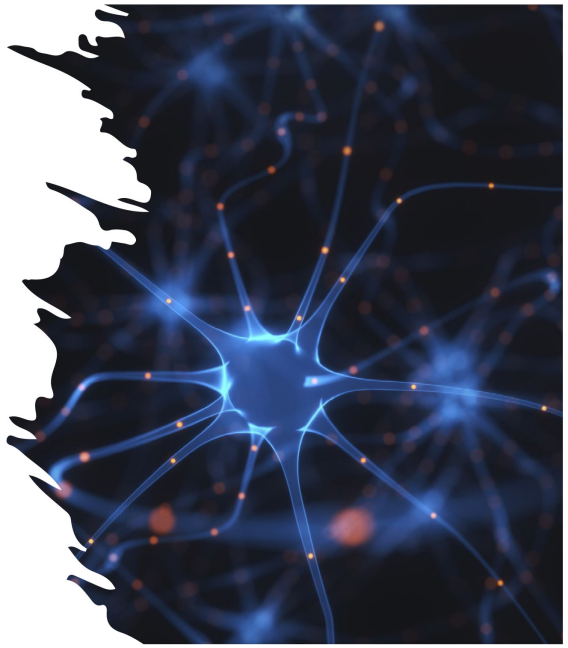
b) What is the prospect of direct benefit that may result from the research and what might this mean?

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

d) Weighing risks against benefits:

- Identifying risks
- Forecasting benefits
  - Benefits to subjects
    - ✓ Direct or indirect
  - Benefits to others
    - ✓ Importance of knowledge, significance of benefits
- Methods for making a determination:
  - 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
- Placebo should not be used when accepted therapy exists

Identifying Risks: Additional Considerations for Social and Behavioral Research

- Risks are often 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 complicates risk assessment

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 adequately inclusive?

d) Are there adequate additional safeguards for potentially vulnerable subjects?

Equitable Selection and Reasonable Risks-Benefits Consideration §46.111(a)(2)

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?

Review Criterion – Informed Consent Will be Obtained and Documented

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

Why is Informed Consent Important for Research?

Respect for people, their desire to have control over their lives.

Purpose is to help people make *informed* decisions about whether to participate.

- **Ethical ideals:**
  - Individuals decide for themselves according to their own values and opinions (autonomy)
    - Voluntariness
    - Informed Consent
  - Those whose autonomy is compromised should be protected
    - Special attention to undue influence and coercion
    - Additional protections

What Information Do Prospective Participants Need?

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)

Communication – Where the Researcher is Coming From and Where the Prospective Subject is Coming From

- People are generally unfamiliar with the concepts of research
- Think about where researchers are coming from, why they want to do the research, and what they hope to find
- Consider how prospective participants might receive and understand the information
- Help prospective participants process and understand the relevance of the information that matters to them
- Decisions to participate in health research, especially therapeutic ones, are complex, private, and usually have great significance to individuals. Be sensitive to this

How You Explain Things Matters – An Example

- *"Randomization means you will be assigned to a group randomly, like the flip of a coin"*

How randomization is done is not as helpful as what it could *mean* to participants. Tell people what randomization *means* to them in the context of research!

- *You cannot choose the group you are in*
- *Assignment not based on what is better for you*
- *You must be okay with being assigned to any of the study groups*
- *If you have a strong preference for one group, you might not want to participate*

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Use Plain Language to Communicate Effectively

- Use common everyday words
- Use shorter words with fewer syllables
- Avoid jargons and uncommon acronyms; explain terms
- Use active voice if possible
- Write it in conversational style
- Use short sentences; keep paragraphs short
- Break up complex concepts into sections

Informed Consent – What Else to Consider

a) Who will obtain informed consent (PI, nurse, other) & in what setting? Is the arrangement conducive to voluntariness and respect for prospective subjects?

b) For research with children, is there appropriate parental permission and child assent?

c) For research with participants with impaired decision-making capacity, is there a plan for including a Legally-Authorized Representative (LAR)?

Review Criterion – 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?

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 & confidentiality issues properly addressed, e.g., use of genetic information?

Additional Requirements for Reviewing Subpart Populations

45 CFR part 46

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

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…

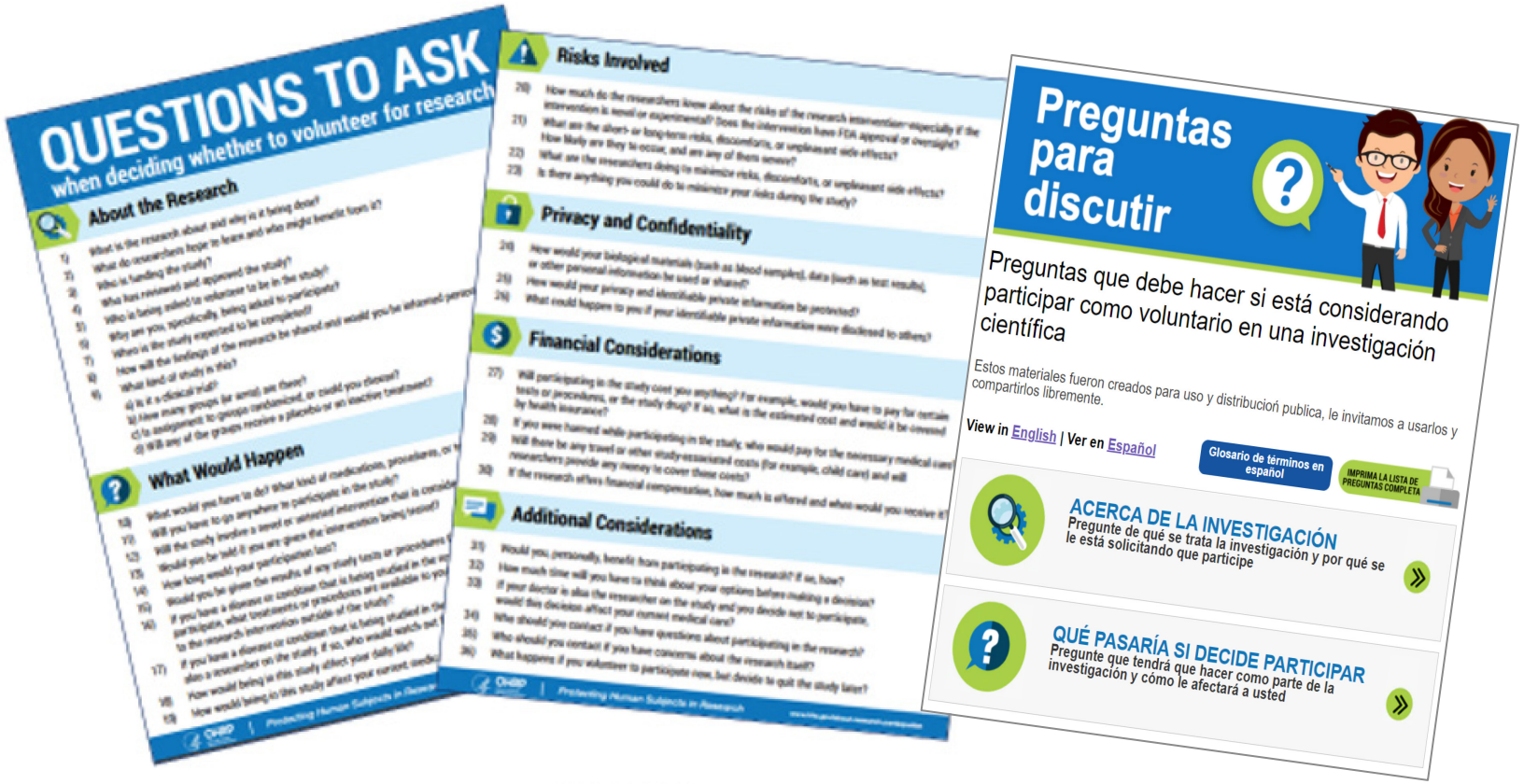
Things to consider:

- 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?

A Shared Responsibility – The Role of Researchers

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

OHRP Public Outreach Resources at
www.hhs.gov/About-Research-Participation
Resources also available in Spanish!



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.
- Watch recorded webinar *Simplifying Informed Consent (with OHRP)* [November 10, 2020]

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Questions?

Thank you!