San Francisco State University:

Regulatory Criteria for Approval and Additional Considerations for Social-Behavioral IRBs

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Agenda

• Belmont Report ethical principles and their relationship to the regulatory criteria for approval of research

• Social/Behavioral Research points of emphasis within the regulatory criteria for approval

• Protocol review guidelines

• Review of each of the regulatory criteria
The Belmont Report and the Regulatory Criteria for Approval
Ethical Principles Governing Human Research

• Three basic principles:
  – Respect for Persons
  – Beneficence
  – Justice

• Outlined by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research
The rules that derive from the Belmont Principles are the regulatory criteria for approval.

**Main Criteria**
(45 CFR §46.111/ 21 CFR §56.111)
(a)(1) – Minimization of risks
(a)(2) – Risk-benefit relationship
(a)(3) – Equitable selection
(a)(4) – Consent process
(a)(5) – Consent documentation
(a)(6) – Data monitoring
(a)(7) – Privacy/confidentiality
(b) – Vulnerable subjects

**Consent Process**
(45 CFR §46.116, 21 CFR §50.20, §50.25)
- Intro – Consent process
  (a)– Required disclosures
  (b)– Additional disclosures
  (c)– Waiver #1
  (d)– Waiver #2

**Consent Documentation**
(45 CFR §46.117, 21 CFR §50.27, § 56.109)
- (a) – General
  (b)(1) – Long form
  (b)(2) – Short form
  (c)(1) – Waiver #1
  (c)(2) – Waiver #2 (Not FDA)
The regulatory criteria for approval contain all of the rules necessary to protect human subjects.

- All are applicable to both Social-behavioral research as well as biomedical research

- Systematically using the regulatory criteria requires thoughtful effort

- There are too many regulatory criteria to memorize
  – Use checklists or other tools as reference guides
Avoid overarching ethical principles when reviewing human research

• Beneficence
  – “This will provide access to superior care unavailable elsewhere.”

• Respect for persons
  – “I don’t see why anyone in their right mind would participate in this. However, everything is in the consent document, and if a person will sign this, it is OK with me.”

• Justice
  – “There is no way that we can approve this study without allowing Spanish speaking subjects. The principle of “justice” demands this.”
IRB review requires an approach that is both systematic and flexible

- Ethical decision making is about systematically considering the regulatory criteria for approval.

- Balance the ethical principles.
  - Avoid overarching ethical principles.

- Meet the criteria while balancing the principles.
  - The regulatory criteria are full of subjective judgment calls: “reasonable,” “adequate,” “sound,” “equitable,” etc.
Social/Behavioral Research points of emphasis within the regulatory criteria for approval
Utilizing the flexibility of the regulations affects points of emphasis in the IRB review process

- Not “Research” involving “Human Subjects”
- Exempt Research
- Expedited Reviews
- Privacy and Confidentiality
- Waiving Consent Documentation
- Issues directed towards “> minimal risk” research:
  - Data Safety Monitoring
  - Risk minimization
Social-behavioral IRBs may still review biomedical research

- FDA definition of “Human Research” differs from DHHS definition
- DHHS exemption categories don’t apply to FDA-regulated research
- Additional regulations must be addressed:
  - 21 CFR 50
  - 21 CFR 56
  - 21 CFR 312
  - 21 CFR 812
- IRB Member who is a licensed physician needed when research involves drugs or devices
Protocol Review Guidelines
Who needs to review the protocol materials?

- Primary reviewer?
- Secondary Reviewer?
- Alternate substituting for another members?
- Unaffiliated member?
- Scientific Member?
- Non-scientific Member?

Everyone
What does it mean when you vote to approve research?

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IRB has determined that all regulatory criteria for approval are met.
When do criteria for review apply?

- Initial review
- Continuing review
- Review of modifications
- Review by a convened IRB
- Review by the expedited procedure
Protecting participants is about remembering to ask the right questions.

- The answers are usually easy
- The questions are difficult to remember
- Use Checklists
The Regulatory Criteria for Approval
Criterion for approval #1:

45 CFR §46.111(a)(1)(i)

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.
Do the regulations say “Risks must be minimized”? 
Two required criteria to minimize risk

• ...By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

• ...Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
Risks to subjects are minimized by using procedures, which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

- Can risks be reduced by changing the research procedures in a way that will still allow the research to get done and will not unnecessarily expose subjects to risk? (Risk = Physical, Social, Psychological, Economic, or Legal)

- Examples:
  - Can less invasive/intrusive methods answer the question?
  - Can fewer procedures answer the question?
  - Can fewer subjects answer the question?
  - Are certain procedures needed at all?
  - Can additional procedures (e.g., monitoring) reduce risk?
  - Can different exclusion criteria reduce risk?
  - Is the research staff qualified?
Risks to subjects are minimized by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- Are procedures that will answer the scientific question being done anyway?

- If so, can the data from these procedures be used to reduce risks? (Risk = Physical, Social, Psychological, Economic, or Legal)
Criterion for approval #2:

45 CFR §46.111(a)(1)(i)

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.
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.

1. What are the risks to subjects? (Physical, social, psychological, economic, legal)
2. What are the anticipated benefits to subjects?
3. What is the importance of the knowledge that may reasonably be expected to result?

Is (1) reasonable in relation to (2) and (3)?
Analysis of risks and potential benefits:
Anticipated benefits and knowledge to result

- Risk to Participants
- Anticipated benefits to participants
- Importance of the knowledge expected to result
Analysis of risks and potential benefits: No benefits
Analysis of risks and potential benefits: No knowledge
Risk benefit analysis:
No benefits and no knowledge
“...the importance of the knowledge expected to result...”

- Will any knowledge result?
  - Good scientific design*
  - Adequate resources
    - Research staff qualifications
    - Adequate time
    - Adequate personnel
    - Adequate participant pool

- What will be its importance?*

*Requires scientific or scholarly expertise
Scientific Review vs. Scientific Validity

- *Detailed* scientific review outside of IRB scope

- Emphasis is on *validity*:
  - Is the research protocol scientifically sound or does it have scholarly merit?
  - Does the protocol accurately describe the research in a clear, detailed way?
  - Is the research likely to answer its proposed question?
  - Does the protocol *fairly portray* the importance of the knowledge expected to result?
  - Is the available background information adequate to support the proposed research?
How do non-scientific members handle scientific issues?

• The IRB review process should explain all the scientific issues to the non-scientific members.

• Non-scientific members should be provided an explanation of:
  – the risks to participants,
  – potential benefits to participants, if any, and
  – the importance of the knowledge expected to result.
Criterion for approval #3:

45 CFR 46.111(a)(3)

Selection of subjects is equitable.
Selection of subjects is equitable.

- Are any subjects unfairlyshouldering the burdens of the research?
- Are any subjects unfairly getting the benefits of the research?

- Consider
  - Purpose of the research
  - Setting of the research
  - Involvement of vulnerable subjects
  - Selection criteria
  - Recruitment, enrollment, and payment procedures.
Criterion for approval #4:

45 CFR 46.111(a)(4)

Informed consent will be sought from each prospective subject or LAR, in accordance with, and to the extent required by [46.116 / Section 5: Consent Process].
Options for criterion for approval #4

- Obtain informed consent as required

- Waive or alter informed consent process
Informed consent process criteria (§46.116)

- Consent will be legally effective.

- Circumstances of the consent process will provide the participant sufficient opportunity to consider whether to participate.

- Circumstances of the consent process will minimize the possibility of coercion or undue influence.

- Information will be given in understandable language.

- No exculpatory language.
The investigator will obtain the *legally effective* informed consent of the subject or LAR.

- Subjects are provided enough information.
  - *Will the elements in Section 7: Elements of Consent Disclosure be disclosed and explained?* 
  - *Will subjects be given additional information when appropriate?*

- Subjects understand the consequences of a decision.

- Subjects are able to make a decision.

- Subjects are able to communicate that decision.
Consent will be obtained only under circumstances that provide the prospective subject or LAR sufficient opportunity to consider whether or not to participate.

- Subjects need enough time to make a voluntary choice.

- Consider:
  - Who is obtaining consent?
  - How much time does each person obtaining consent expect to devote and have available to devote to the consent process?
  - What is the time window between the initial consent request and when the subject will have to make a decision whether or not to take part?
Consent will be obtained only under circumstances that minimize the possibility of coercion or undue influence.

- Subjects must be in a position to make a voluntary choice.
  - Coercion – person has no choice
  - Undue influence – inappropriate influence. Appropriate influence is acceptable.

- Consider:
  - Where will consent be done?
  - What is the relationship of the person obtaining consent to the subject?
  - What steps will be taken to make sure the subject does not feel pressured?
“Influence” vs. “Undue Influence”

• Influence is acceptable (e.g., payment for participation)

• Undue influence is not acceptable

• Special issues of influence include advertisements and payment for participation.
  – See toolkit worksheets for additional information
Information to be given to the subject or LAR will be in language understandable to them.

- “Readability” is neither necessary nor sufficient: It is about all communications in the consent process.

- Will the research team communicate with the subject in a way that the subject will understand the information?

- Consider:
  - What language do the subjects speak?
  - What is the educational level of the subjects?
  - Can the research team communicate in understandable language to the participants or representatives?
  - Will written information be in the language understandable to the participants or representatives?
There is no exculpatory language.

• Is there any language through which the subject waives or appears to waive his or her legal rights?

• Is there any language through which the subject releases or appears to release the investigator, the sponsor, the institution or its agents from liability from negligence?

• Examples:
  – Compensation will not be provided for lost wages or disability
  – No other compensation will be provided
  – (Stating “You have not waived your legal rights” does not make the above statements true)
Examples of Non-exculpatory language include the following:

• No commitment is made to provide other compensation.

• No money has been set aside to provide other compensation.

• We have no policy to provide other compensation.

• No provisions have been made to provide other compensation.

• State law may limit the compensation we can provide.
Options for criterion for approval #4

- Obtain informed consent as required.
- Waive or alter informed consent *process*.
# Mechanisms for Waiver of Consent

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>DHHS</th>
<th>FDA</th>
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<tr>
<td>Demonstration projects</td>
<td>45 CFR 46.116(c)</td>
<td>N/A</td>
</tr>
<tr>
<td>Research not practicable</td>
<td>45 CFR 46.116(d)</td>
<td>N/A</td>
</tr>
<tr>
<td>Emergency exception</td>
<td>N/A</td>
<td>21 CFR 50.23(a)-(c)</td>
</tr>
<tr>
<td>Presidential waiver</td>
<td>N/A</td>
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<td>Planned emergency waiver</td>
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</tr>
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<td>Anonymous tissue</td>
<td>N/A</td>
<td>Guidance issued April 25, 2006</td>
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Waiver or Alteration of the Consent Process may be granted under (45 CFR §46.116(d)) if the IRB is able to find and document the following:

- The research is NOT FDA-regulated.
- The research does NOT involve non-viable neonates.
- The research involves no more than minimal risk to the subjects.
- The waiver or alteration will NOT adversely affect the rights and welfare of the subjects.
- The research could NOT practicably be carried out without the waiver or alteration.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
Criterion for approval #5:

45 CFR 46.111(a)(5)

Informed consent will be appropriately documented, in accordance with, and to the extent required by [46.117 / Section 6: Long Form Of Consent Documentation]
Options:

• Obtain written documentation of consent using the “long form” (a.k.a. standard informed consent template).

• Obtain written documentation of consent using the “short form.”

• Waive the requirement for written documentation of consent.
Informed consent will be appropriately documented, in accordance with, and to the extent required by Section 6: Long Form Of Consent Documentation.

- Is the consent form accurate and complete?
  - Does the consent form include the elements in Section 7: Elements of Consent Disclosure?

- Will the investigator give the subject adequate opportunity to read the consent form?

- Will the subject sign and date the consent form?

- Will the person obtaining consent sign and date the consent form?
Informed consent will be appropriately documented, in accordance with, and to the extent required by Section 6: Long Form Of Consent Documentation

- Will a copy of the signed and dated consent document will be given to the person signing the document?

- If there is an LAR or parent signature line, has the IRB approved inclusion of adults unable to consent or children?

- When a subject or LAR is unable to read: Will an impartial witness be present during the entire consent discussion and will the consent document note that the witness attests that the information in the consent document and any other information provided was accurately explained to, and apparently understood by, the subject or the subject's LAR, and that consent was freely given?
Options:

• Obtain written documentation of consent using the “long form” (a.k.a. standard informed consent template).

• **Obtain written documentation of consent using the “short form.”**

• Waive the requirement for written documentation of consent.
Obtain written documentation of consent using the “short form.”

- The written consent document states that the elements of consent have been presented orally to the subject or the subject’s LAR.
- There is written summary of what is to be said to the subject or the LAR that embodies the required and appropriate additional elements in Section 7: ELEMENTS OF CONSENT DISCLOSURE.
- The consent document and summary are accurate and complete.
- An impartial witness is present during the entire consent discussion.
- For subjects who do not speak English the witness is conversant in both English and the language of the subject or the subject’s LAR.
- The subject or the subject’s LAR will sign and date the consent document.
Obtain written documentation of consent using the “short form.”

- When a subject or the subject's LAR is unable to read:
  - An impartial witness will be present during the entire consent discussion and the consent document notes that the witness attests that the information in the consent document and any other information provided was accurately explained to, and apparently understood by, the subject or the subject's legally authorized representative, and that consent was freely given.

- The witness will sign and date the summary.

- The person obtaining consent will sign and date the summary.

- A copy of the summary will be given to the person signing the document.

- A copy of the signed and dated consent document will be given to the person signing the document.

- If there is a signature line for a LAR or parent, the IRB has approved inclusion of adults unable to consent or children.
Options:

• Obtain written documentation of consent using the “long form” (a.k.a. standard informed consent template).

• Obtain written documentation of consent using the “short form.”

• Waive the requirement for written documentation of consent.
Waive the requirement for written documentation of consent: 45 CFR §46.117(c)(1)

- The research is not FDA-regulated.
- The written script of the information to be provided orally and all written information to be provided include all required and appropriate additional elements of consent disclosure in Section 7: ELEMENTS OF CONSENT DISCLOSURE.
- The only record linking the subject and the research would be the consent document.
- The principal risk of a signed consent document would be the potential harm resulting from a breach of confidentiality.
- Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject’s wishes will govern.
Waive the requirement for written documentation of consent: (21 CFR §56.109(c)(1) and 45 CFR §46.117(c)(2))

- The written script of the information to be provided orally and all written information to be provided include all required and appropriate additional elements of consent disclosure in Section 7: ELEMENTS OF CONSENT DISCLOSURE.

- The research presents no more than minimal risk of harm to subjects.

- The research involves no procedures for which written consent is normally required outside of the research context.
Criterion for approval #6

45 CFR 46.111(a)(6)

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

• Not needed if minimal risk

• If more than minimal risk:
  – Is someone looking at the collected data with enough frequency and depth to make sure that if subjects as a group are at a greater risk than originally expected something will be changed to address that risk?

• Consider:
  – *Who reviews the data?*
  – *What data are reviewed?*
  – *When are data reviewed?*
Who reviews the data?

- Investigator
- Internal associate
- Medical monitor
- Internal committee
- Independent committee (DSMB)
- IRB
What data are reviewed?

• Safety data
  – Untoward events
  – Serious adverse events
  – IND safety reports

• Efficacy data
When are data reviewed?

- On-line
- Every $X$ subjects
- Monthly, Quarterly, Annually…
Criterion for approval #7

45 CFR 46.111(a)(6)

When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
Privacy vs. Confidentiality

• Not the same thing

• Privacy:
  – About people
  – Right
  – Protected

• Confidentiality
  – About data
  – Agreement
  – Maintained
Privacy interests refer to a person’s desire to control how, and with whom, they interact and communicate, particularly on issues that may be “sensitive” or “private.”

• Privacy refers to persons and their interest in controlling “access to themselves.”

• Access could be through:
  – Interventions
  – Interactions
  – Collecting of information
There are adequate provisions to protect the *privacy* of subjects.

• Are the procedures in the research adequate to ensure that subjects’ expectations of privacy will be met?

• Consider:
  – Comfort with the procedures being performed.
  – Comfort with the research setting.
  – Comfort with the information sought.
Example of privacy issues

- Children want parents to be present
- Teenagers want parents to be absent
- People want to talk to the same gender
- Setting of interactions (Office, hallway, phone)
- Type of interaction (survey, physical exam)
- Method of data collection (hidden camera)
When appropriate, there are adequate provisions to protect the privacy of subjects

Q: When are provisions to protect the privacy of participant “appropriate”?

A: When participants have an expectation of controlling access to themselves.
There are adequate provisions to maintain the *confidentiality* of data.

• Are the procedures in the research adequate to meeting the investigator’s promises to limit release of the data?

  – Privacy is about **PEOPLE** and refers to persons and their interest in controlling access to themselves.

  – Confidentiality is about **DATA** and refers to agreements with the subject about how data are handled.
When appropriate, there are adequate provisions to maintain the confidentiality of data.

**Q:** When are provisions to maintain confidentiality “appropriate”?

**A:** When confidentiality is pledged; OR when there are legal/ethical requirements.
How do you determine that there are adequate provisions to maintain the confidentiality of the data?

- What *promises* have been made about the collected data?

- What *procedures* are in place to meet those promises?
  - What information is included in the data?
  - How is it stored?
  - How long will it be stored?
  - Who has access to it?
  - Who is responsible for receiving/transmitting it?
What are provisions to maintain confidentiality of data?

- Restricted access (Locks/passwords)
- Certificates of confidentiality
- Error inoculation/Random responses
- Bracketing/Top coding
- Ethical editing of qualitative descriptions
- Data brokering
Criterion for approval #8

45 CFR 46.111(b)

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
Who is vulnerable to coercion and undue influence?

- Fetuses
- Neonates of uncertain viability
- Non-viable neonates
- Prisoners
- Children
- Handicapped
- Mentally disabled persons
- Economically disadvantaged
- Educationally disadvantaged
- Students
- Employees
- Life threatening disease
How do you determine whether there is a vulnerable population?

- Is there a power differential?
- Are there communication issues?
- Are there decisional issues?
- Are there excessive motivating factors?
- Is the recruitment process acceptable?
- Are advertisements acceptable?
- Are payment arrangements acceptable?
IRB Members need to consider these general issues when reviewing research involving vulnerable populations.

- The research is of importance to the vulnerable population.
- The research question cannot be answered by using a non-vulnerable population.
- The risk-potential benefit relationship is appropriate to the vulnerable population.
- Additional steps will be taken to minimize coercion and undue influence of the vulnerable population, when appropriate.
Additional steps to minimize coercion and undue influence

• Assessment of capacity
• Permission of a representative
• Assent
• Witness to the consent process
What are additional safeguards to protect the rights and welfare of vulnerable populations?

- Fetuses and neonates
  - DHHS 45 CFR §46 Subpart B

- Prisoners
  - DHHS 45 CFR §46 Subpart C
  - Dept of Justice 28 CFR 512 Subpart B

- Children
  - DHHS 45 CFR §46
  - FDA 21 CFR §50/56 Subpart D
  - Dept of Education 34 CFR 97 Subpart D
Additional criteria for specific populations

- Children
- Pregnant women
- Prisoners
- Adults unable to consent

Criteria are present in toolkit checklists
Other considerations
Minimal risks

- Does the research involve more than minimal risk to subjects?
  - 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 of normal persons or during the performance of routine physical or psychological examinations or tests in normal persons.
Additional actions

• Initial and continuing review:
  – Should review take place more often than annually? If so, specify period.

• Continuing review:
  – Is verification needed from sources other than the investigator that no material changes have occurred since prior IRB review? (Are there questions about the veracity of the information provided is questioned.)

• Continuing review and modifications:
  – Is there information that needs to be provided to current or former subjects because it may affect their willingness to continue participation?
Recruitment

- Do advertisements meet WORKSHEET: Advertisements criteria?
- Do payments to subjects meet WORKSHEET: Payments criteria?
Thank You!

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Human Research Protection Program Toolkit:
www.hrpppsops.com