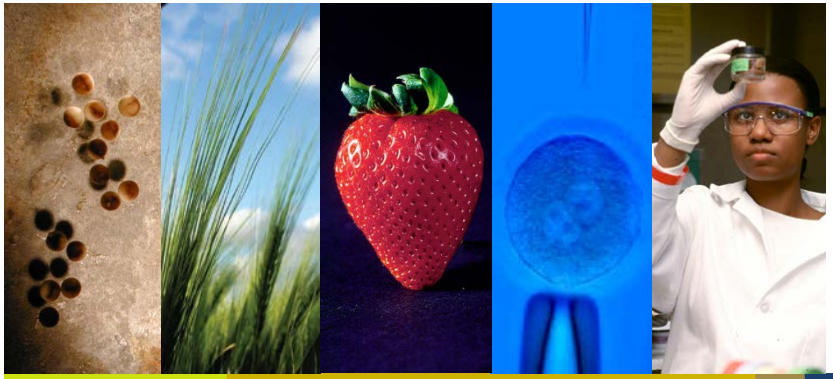

Overview of the Criteria for Approval of Research

Miles McFann
IRB Administration
mtmcfann@ucdavis.edu
Original Presentation Created by
Jeffrey Cooper, M.D.

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Overview of Research Ethics and Regulation

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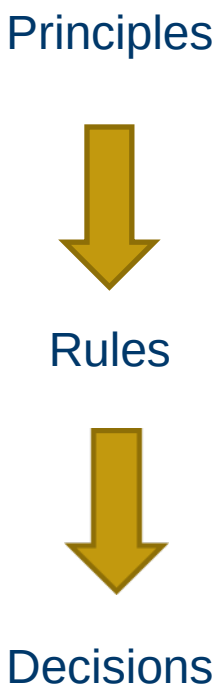
Ethical Decision Making

- Start with fundamental ethical principles
- From the ethical principles derive specific rules.
- When making specific decisions systematically considering each of the rules that derive from each of the ethical principles.



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Ethical Principles Governing Human Research

- Outlined by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research
- Three basic principles
  - Respect for Persons
  - Beneficence
  - Justice

Respect for Persons

- Treat individuals as autonomous agents
- Do not use people as a means to an end
- Allow people to choose for themselves
- Give extra protection to those with limited autonomy

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Beneficence

- Acts of kindness or charity that go beyond duty
- Obligations derived from beneficence
  - Do no harm
  - Prevent harm
  - Prevent evil
  - Promote good

Justice

- Treat people fairly
- Fair sharing of burdens and benefits of research
- Distinguish procedural justice from distributive justice

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Criteria for IRB approval of research

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Criteria for the Approval of Research

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 IRB must determine that criteria delineated in <u>all three boxes</u> are met.

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Regulatory criteria for approval
Readings

- 45 CFR §46.111(a)

- 21 CFR §56.111(a)

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Who needs to make the criteria for approval determination?

- Everyone present at the convened meeting is responsible to determine whether the regulatory criteria for approval are met.
- All criteria can be considered by both scientific and non-scientific members.
- The criteria assume that all members are provided sufficient information to understand the research.
- The determinations required are judgments: “reasonable,” “adequate,” “sound,” “equitable,” etc.

What information does the reviewer need to review?

- Purpose
- Background
- Setting of the research
- Resources available to conduct the research
- Study design
  - Recruitment
  - Inclusion and exclusion criteria
  - Procedures involved in the research
  - Data management
  - Provisions to monitor the data collected to ensure the safety of participants
- Risks to participants
- Potential benefits to participants
- Provisions to protect the privacy interests of participants
- Provisions to maintain the confidentiality of the data
- Consent process
- Process to document consent
- Additional protections for vulnerable populations

Protecting participants is about remembering to ask the right questions.

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Does this seem familiar?

- IRB is inconsistent and arbitrary
- At times IRB is picky
- At times IRB misses critical issues
- IRB is risk averse with low risk research
- One assertive member overly influences other members
- IRB disagrees on key issues but all votes are unanimous

How to run an IRB meeting

1. Expect all members to review the summary of the primary reviewer and use the criteria for approval worksheet in advance of the meeting
   - Abstain if insufficient review
2. Go through criteria serially and focus on one at a time
   - Defer discussion of other criteria until current one is resolved
3. Justify every concern or request with a criterion
   - If no criterion is affected concern/request is off the table
4. Each member votes to approve only if that individual agrees that all criteria are met.

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Contingent approval

- By IRB approval with conditions, OHRP means that at the time when the IRB reviews and approves a research study (or proposed changes to a previously approved research study), the IRB requires as a condition of approval that the investigator:

  a) make specified changes to the research protocol or informed consent document(s),

  b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or

  c) submit additional documents,

  such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46.

- **Translation: IRB describes the protocol that will meet the regulatory criteria for approval**

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Unacceptable contingent approval

- Clarify whether the dose is 10 mg or 15 mg
- Describe all risks of cyclophosphamide
- Provide more information about the data and safety monitoring plan
- Clean up the consent document to make it understandable
- Clarify the schedule and timing of subjects payments
- Justify why you are excluding children
- Describe additional protections for vulnerable subjects

Criterion for approval #1

Criterion for approval #1

- 45 CFR §46.111(a)(1)

- 21 CFR §56.111(a)(1)

Risks to subjects are minimized by using procedures, which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

What is the ethical principle?

What is minimal risk?

45 CFR 46.102(i)
21 CFR 56.102(i)

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

What is a risk?

- Probability and magnitude of harm
- Two factors
  - Probability
  - Magnitude
- If unknown, get consultation
- Each factor or both can be minimized

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

Describe changes that can be requested to protocols in order to minimize risk by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

Criterion for approval #2

Criterion for approval #2

- 45 CFR §46.111(a)(2)

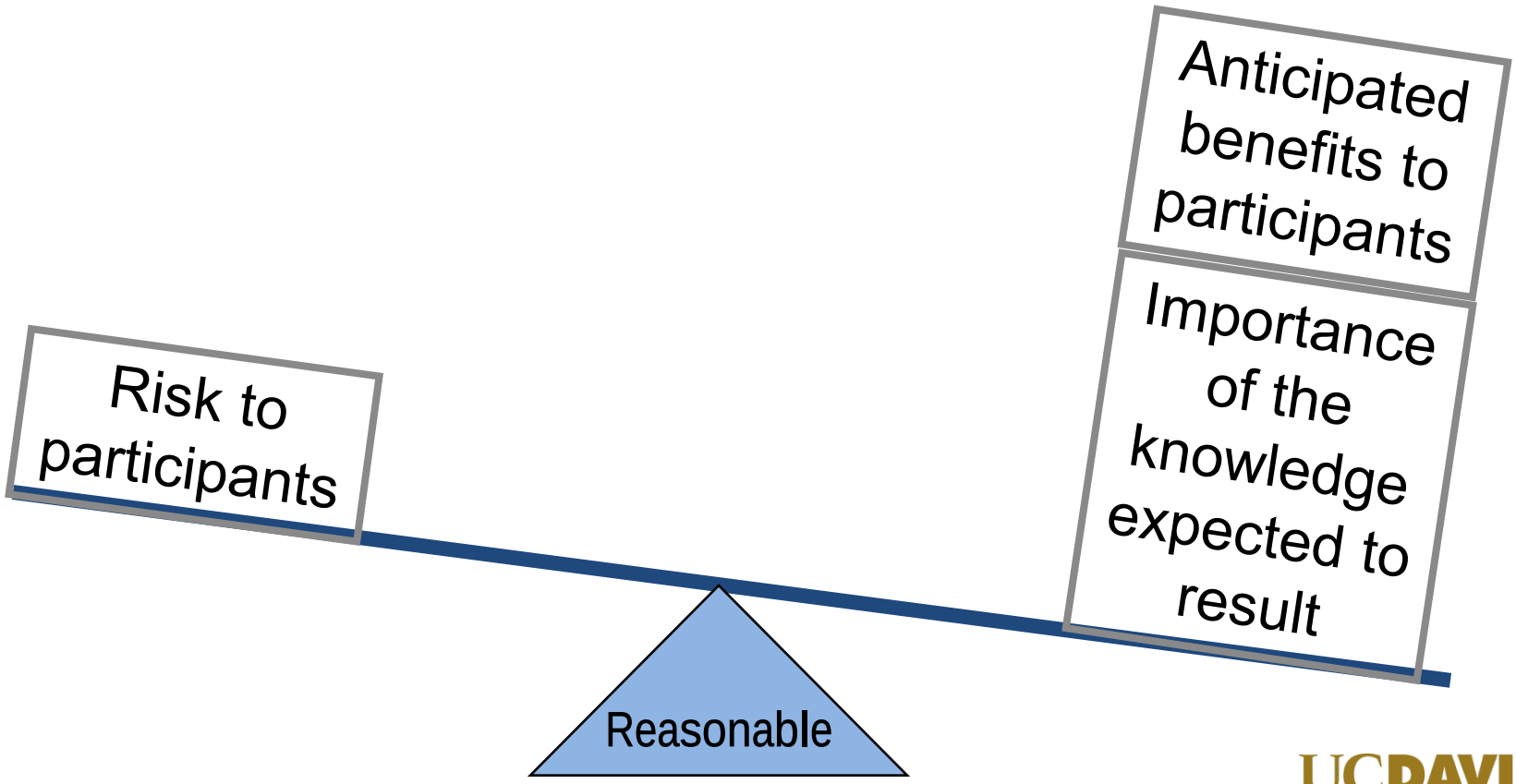
- 21 CFR §56.111(a)(2)

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.

These risks cannot be minimized. Now we have to evaluate if it is ok to have research with these risks.

What is the ethical principle?

Analysis of risks and potential benefits



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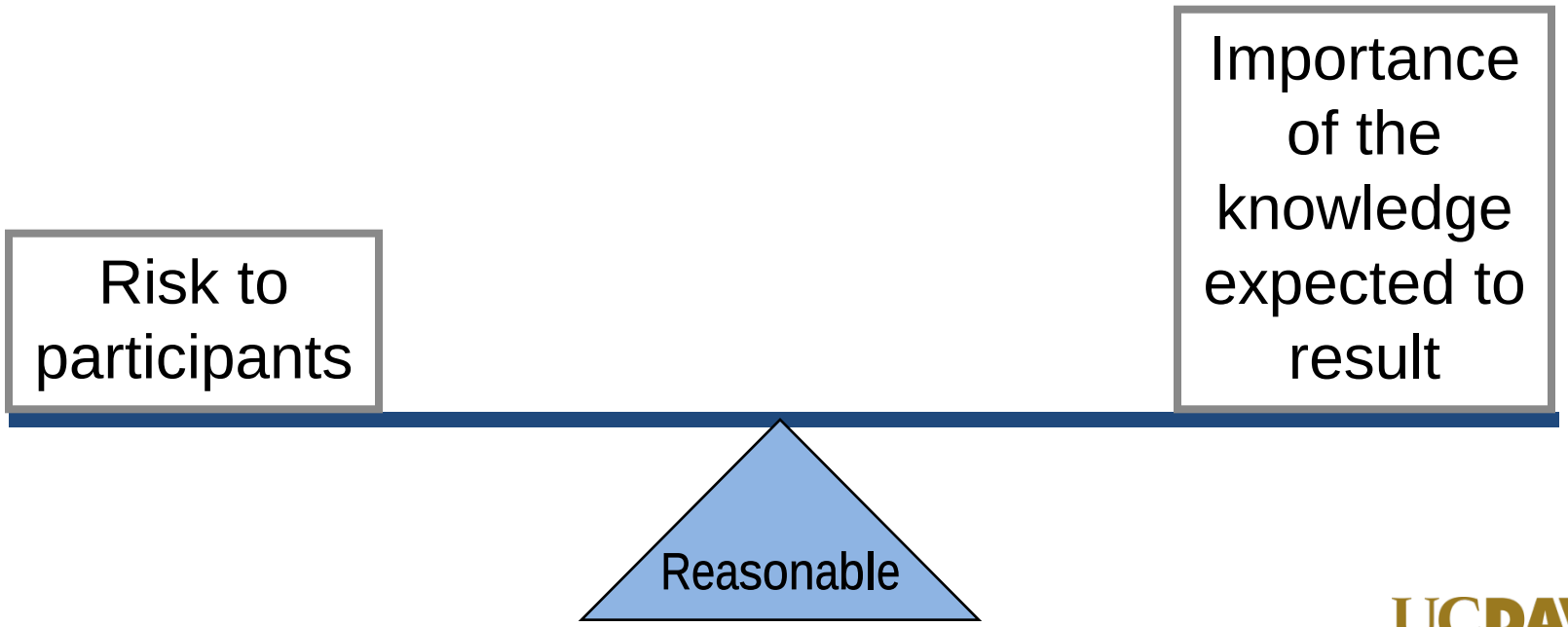
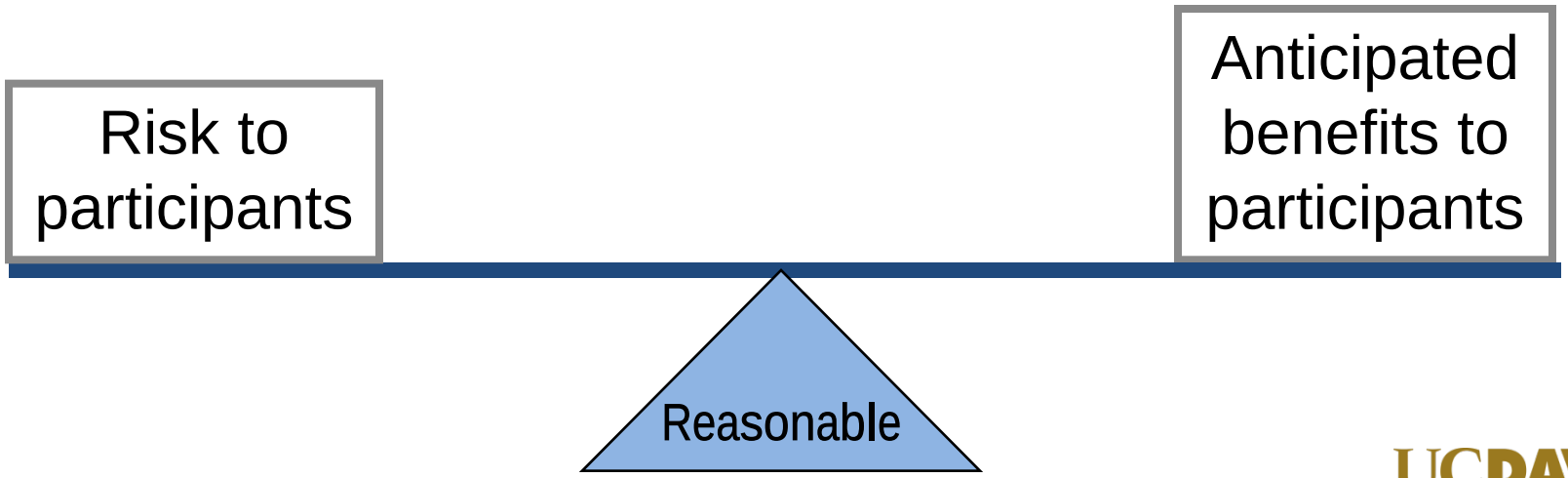
Analysis of risks and potential benefits
No benefits



Analysis of risks and potential benefits
No knowledge



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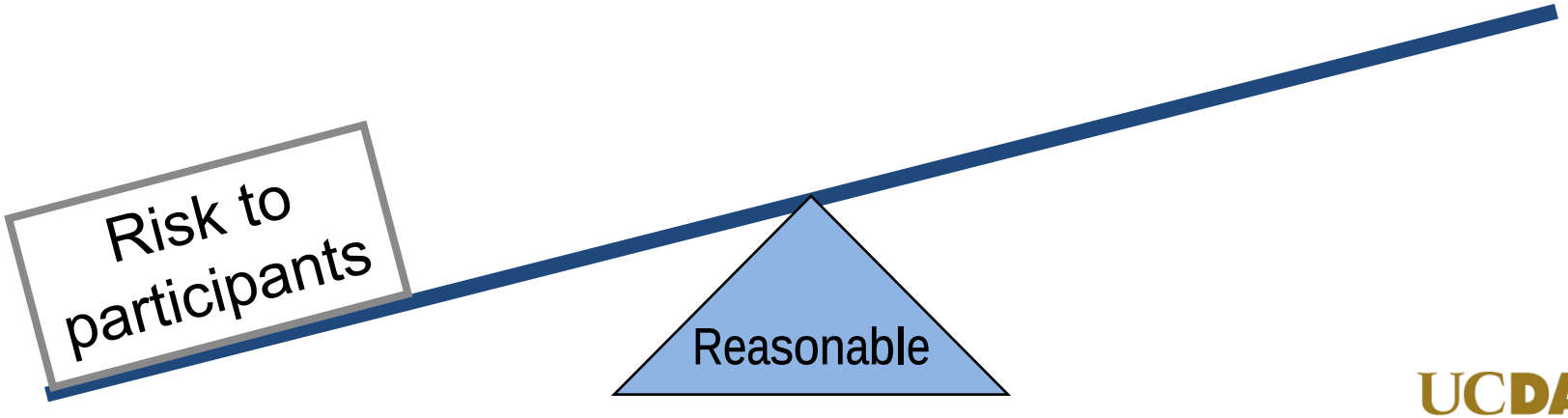
Risk benefit analysis:
No benefits and no knowledge



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How do you answer these questions?

- What are the ***risks to participants***?
- What are the ***anticipated benefits to participants***?
- What is the ***knowledge that may reasonably be expected to result***?

How do you answer these questions?

- Are the risks ***reasonable*** in relationship to benefits?
- What is the ***importance*** of knowledge that may reasonably be expected to result?

What information do you need to review?

- Background
- Study design
  - Inclusion and exclusion criteria
  - Procedures involved in the research
- Risks to participants
- Potential benefits to participants
- Additional protections for vulnerable populations

Criterion for approval #3

Criterion for approval #3

- 45 CFR §46.111(a)(3)

- 21 CFR §56.111(a)(3)

Selection of subjects is equitable.

What is the ethical principle?

Equitable selection

- Fair
- Just
- Burdens distributed fairly
- Benefits distributed fairly
- No population is unfairly targeted
- No population is unfairly excluded

Who might be treated unfairly?

What information do you need to review to determine whether selection of subjects is equitable?

Criterion for approval #6

Criterion for approval #6

- 45 CFR §46.111(a)(6)
- 21 CFR §56.111(a)(6)

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

What is the ethical principle?

Forms of monitoring

- Monitoring of individual subject safety
- Monitoring the conduct of the research
- Monitoring of the data collected

Data safety monitoring plans

- Who reviews the data?
- What data are reviewed?
- When are data reviewed?

When is it appropriate to require monitoring of the data collected to ensure the safety of participants?

What information do you need to review?

- Procedures involved in the research
- Provisions to monitor the data collected to ensure the safety of participants

Criterion for approval #7

Criterion for approval #7

- 45 CFR §46.111(a)(7)
- 21 CFR §56.111(a)(7)

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

What is the ethical principle?

What is the difference between privacy and confidentiality?

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Privacy is about people

Confidentiality is about data

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Privacy versus confidentiality

- Privacy refers to persons and their interest in controlling access to themselves.
- Confidentiality refers to agreements with the participant about how data are to be handled.

Privacy versus confidentiality

Privacy

- About people
- Right
- Protected

Confidentiality

- About data
- Agreement
- Maintained

Criterion for approval #7: Privacy

Privacy

- Privacy refers to persons and their interest in controlling access to themselves.

- Access could be through:
  - Interventions
  - Interactions
  - Collecting of information

Example of privacy issues

- Children want parents to be present
- Teenagers want parents to be absent

What are some other examples of privacy issues in research that do not involve information?

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When appropriate there are adequate provisions to protect the privacy of subjects

- When are provisions to protect the privacy of participant “appropriate”?
  - When participants have an expectation of controlling access to themselves.

- Access could be through:
  - Interventions
  - Interactions
  - Collecting of information

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Criterion for approval #7: Confidentiality

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Confidentiality

- Confidentiality refers to agreements with the participant about how data are to be handled.

  - "I will only share this information with …"
  - "I will not share this information with …"

When appropriate there are adequate provisions to maintain the confidentiality of data

- When are provisions to maintain confidentiality "appropriate"?
  - When confidentiality is pledged; OR
  - When there are legal/ethical requirements.

- Not about risk of harm. (What criterion is this?)

What are provisions to maintain confidentiality of data.

Criterion for approval #8

Criterion for approval #8

- 45 CFR §46.111(b)
- 21 CFR §56.111(b)

Additional safeguards have been included in the study to protect the rights and welfare of subjects vulnerable to coercion or undue influence.

What is the ethical principle?

What is a vulnerable population?

How to 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?

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
- Patients

General considerations for 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

Additional criteria for specific populations

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

Criteria are present in checklists

Criterion for approval #4

Criterion for approval #4

- 45 CFR §46.111(a)(4)
- 21 CFR §56.111(a)(4)

The informed consent process is adequate

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What is the ethical principle?

Options for criterion for approval #4

- Obtain informed consent as required
- Waive or alter informed consent process

Informed consent process criteria

- 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

Legally effective consent

- The person has been provided enough information to make a decision
- The person understands the consequences of a decision
- The person can make a decision
- The person can communicate that decision

Coercion

- The use of express or implied threats of violence, reprisal, or other intimidating behavior to compel a person to act against his or her will
- Under coercion a person has no choice

Undue influence

- Influence: To produce an effect on by imperceptible or intangible means; to sway
- Undue: Exceeding what is appropriate or normal; excessive

Influence versus undue influence

- The regulations allow influence that is not undue.
- The regulations do not prohibit undue influence but require that it be minimized.

Special issues of influence

- Worksheet: Advertisements
- Worksheet: Payment for participation

Criterion for approval #4

- The information that will be given to the participant or the representative will be in language understandable to the participant or the representative

Understandable language

- What language do the participants or representatives speak?
- 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?

What is exculpatory language?

Exculpatory definition

- Language that has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt.
- **Exculpatory:** Waive right to be compensated for injuries arising from participation in the research.
- **Not exculpatory:** Waive right with respect to a biospecimen obtained by investigators for research purposes.

Exculpatory language

- If you suffer a research-related injury, neither the institution nor the investigator can assume financial responsibility or liability for the expenses of treatment for such injury.
- In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer.
- (Stating “You have not waived your legal rights” does not make the above statements true)

Non-exculpatory language

- Although future research that uses your samples may lead to the development of new products, you will not receive any payments for these new products.
- Because of hospital policy, the hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be either covered by the University or the study Sponsor or may be billed to your insurance.

Criterion for approval #4
Elements of consent disclosure

- 45 CFR §46.116(a) and (b)

- 21 CFR §50.25(a) and (b)

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Frequently missed elements

- A statement that the study involves research
- Whom to contact in the event of a research-related injury to the subject
- Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled

Frequently missed element

- A statement that the particular treatment or procedure may involve risks to the subject which are currently unforeseeable
- A statement that if the participant is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject

What information do you need to review?

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Criterion for approval #5

Criterion for approval #5

- 45 CFR §46.117
- 21 CFR §50.27

The documentation of informed consent is adequate

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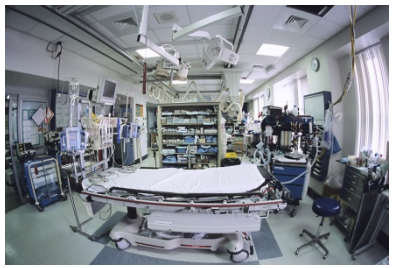
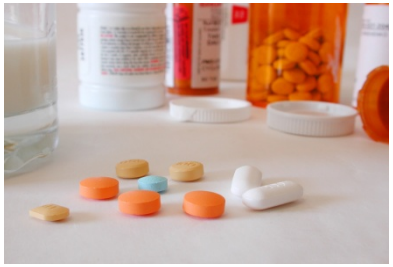
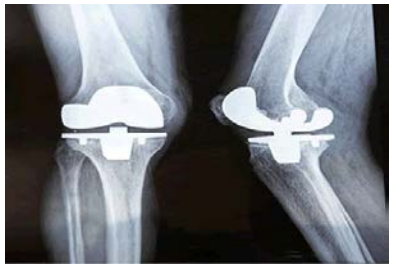
What is the ethical principle?

Overview of the Criteria for Approval of Research

Miles McFann

IRB Administration



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