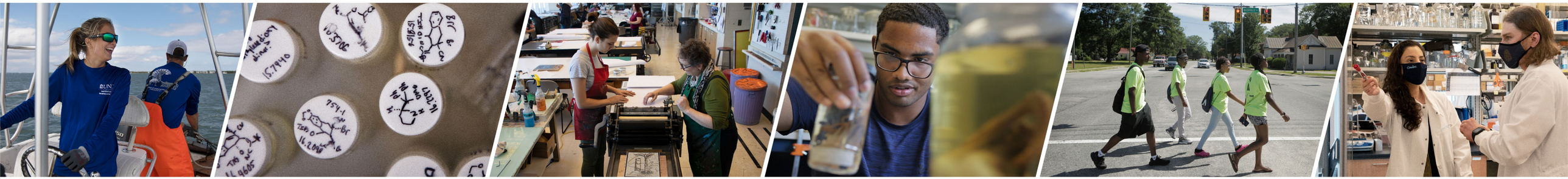
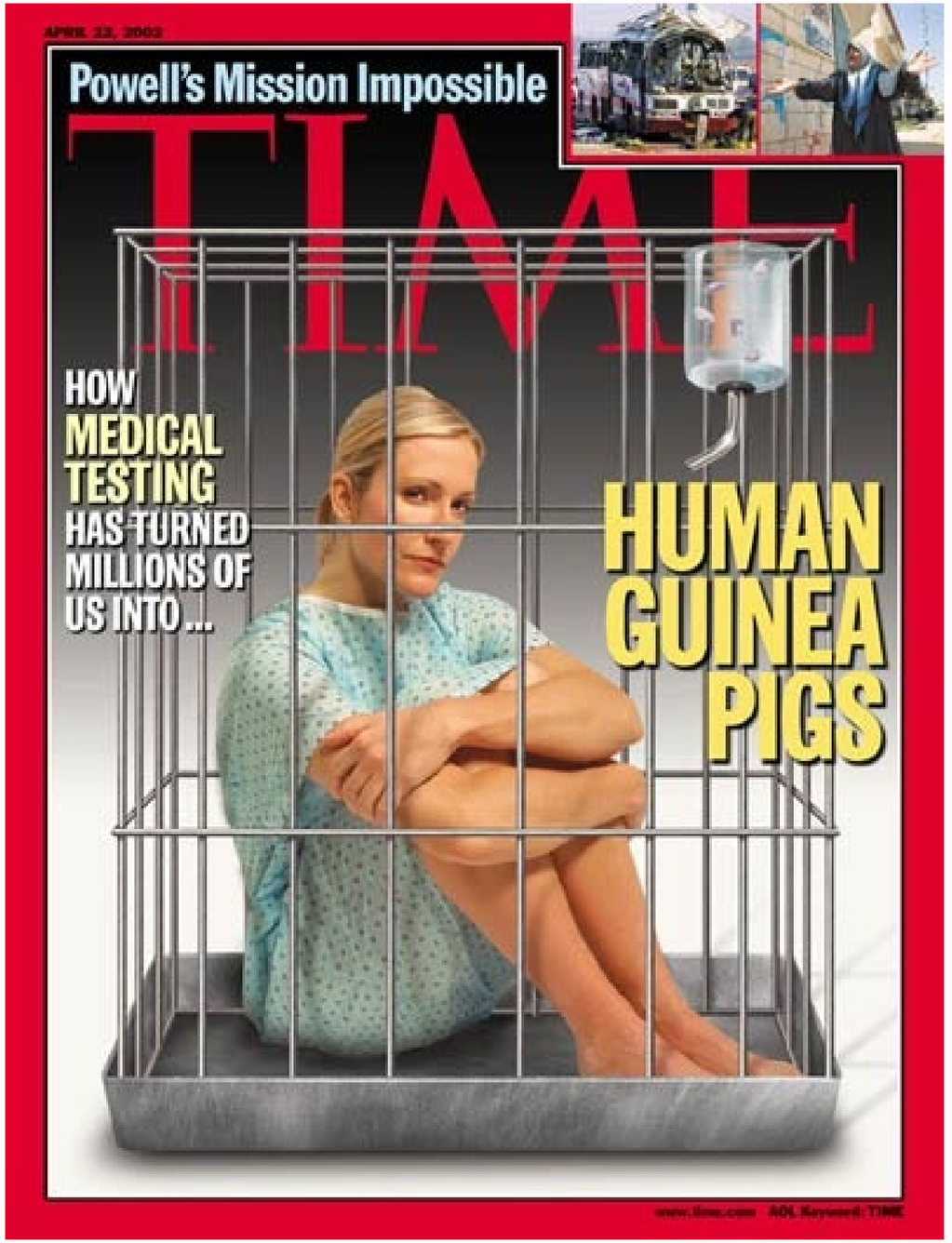
45 CFR 46.111, 112, 113 & 114



UNC | RESEARCH

Presentation Topics

- § 46.111 – Criteria for Approval
- § 46.112 – Review by Institution
- § 46.113 – Suspension or Termination of IRB Approval of Research
- § 46.114 – Cooperative Research



(2022, April 22). TIME, 159(16).

Belmont Report & 45 CFR 46.111 & 21 CFR 56.111

1. Risks minimized	Respect for Persons & Beneficence
2. Favorable risk : benefit ratio	Respect for Persons & Beneficence
3. Equitable selection of subjects	Justice
4. Informed consent sought	Respect for Persons
5. Informed consent documented	Respect for Persons
6. Monitoring plan for safety	Beneficence
7. Privacy & confidentiality protected	Respect for Persons
8. Additional safeguards for vulnerable populations	Respect for Persons, Beneficence & Justice

§46.111 & §56.111

a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
   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.

Criteria 2: The Most challenging of the List

Risk for sick & healthy children? Well Child standard.
CAPA: Y/N?
Which
Vulnerable
Group?
Why?
Really??
Cat 9?
SAE?
Benefits?
What?
To Whom?
How many parental signatures?
UPIRSO

§46.111 & §56.111 (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.

In evaluating risks and benefits, the IRB should consider **only those risks and benefits that may result from the research** (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

The **IRB should not consider** possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

Key Words

- Reasonable ⟹ Benefits
- Reasonability ⟹ Results, data, knowledge
- Limit risks to those of the research only, not treatment
- Can not consider any potential long-range possible policy applications
- Benefit is not any remunerations offered
- Can research be done without inclusion of vulnerable populations?

IRB Makes a Risk Determination or Assessment When You Vote to…

- Approve a study (& it's design); protocol amendment; waiver of consent element(s) or documentation & every Cat 9
- Decide the child research risk level -- 404, 405 which requires 1 parent signature or 406 which requires both parents' signature*
- Decide if an event is a serious, a serious adverse event, a UPIRTSO, non-compliance, serious non-compliance, continuing serious non-compliance
- If the Corrective Action Plan (CAPA) is appropriate to prevent renewed risk to subjects

*Unless 1 parent is deceased, unknown, incompetent, not reasonably available, or only 1 parent has legal custody.

§46.111 & §56.111 (3) “Selection of Subjects is Equitable”

IRB responsibility

- Purpose of research
- Research setting
- Does it include subjects vulnerable to coercion or undue influence?
  - Children
  - Prisoners
  - Impaired decision-making capacity
  - Economically or educationally disadvantaged

Factors to Consider

- Sex of animals & people
- Ethnic groups
- Genetic factors
- Age differences
- What is the target population for this drug/device?

Considerations for the IRB

- Appropriate balance of male & female subjects
- Provisions for consent in other languages & staff with those same abilities to answer questions
- Will minors be enrolled?
  - Is that appropriate?
- Recruitment strategy appropriate & thorough?

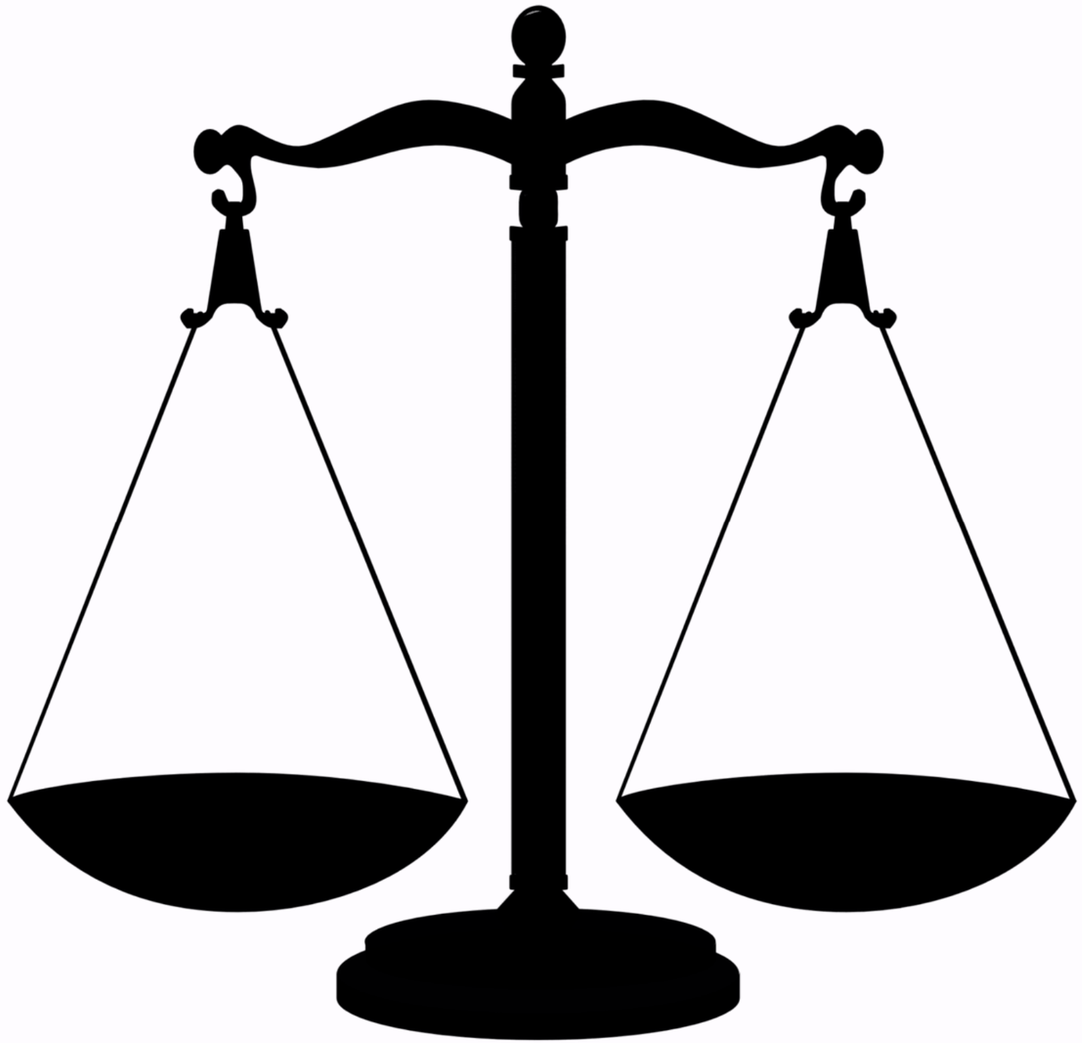
Belmont & Informed Consent

- People are autonomous
  - Freedom to choose based on:
    - Information about the study
    - Comprehension
    - Voluntary to join, remain in the study & leave at anytime

Don’t Forget…

- Consent is an on-going process, not an event
- “in language understandable to the subject”: Foreign Language Consents, Braille, illiterate subjects
- Emergency Care Research & Emergency Research
- Competency: temporary, permanent, on a continuum
- Legally Authorized Representatives
- HIPAA & Research

Belmont & Safety Plan (Beneficence)



45 CFR 46.111 (6)

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

Why is this necessary?

- Is the study on track?
  - Will it be able to answer the research question?
  - Will it not be able to answer the research questions & need to stop?
- Are the risks what was anticipated?
- Have they changed?
  - Increased in severity &/or frequency?
- Are stopping rules in place & appropriate?

How to Monitor & Who Does It

Safety Plan should match the risks posed.

Range of options

- Data Monitor – independent reviewer
- Data Monitoring Committee
- Chartered Data Safety Monitoring Board

Note: NIH funded trials require a Data & Safety Monitoring Plan & some a DSMB

Scientific Review Committee (SRC)

Review study protocols prior to IRB submission that meet the following:

- Greater than minimal risk
- Have not received rigorous scientific review
- Are not cancer research
- Not a local site of a multi-center industry sponsored study

Require submission of a “comprehensive protocol written to accepted industry standards”

45 CFR 46.111 (7)

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

Privacy: Individual private information

- The state or condition of being free from being observed or disturbed by other people.
- The state of being free from public attention.

Confidentiality: Protection of private data

- The state of keeping or being kept secret or private.

UNC SOP 1901: Information Security

Provisions for Data Security must be described in applications to the IRB and updated as necessary.

When information containing direct identifiers such as social security numbers or PHI including data considered sensitive is to be transferred outside of the institution, the provisions for data security may be subject to further review and approval by the by School IT Directors (also the Information Security Liaison) in consult with ITS Security.

UNC SOP 2601: Certificate of Confidentiality (CoC)

- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have **adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.**

- CoC protects against forced disclosure; however, subjects can voluntarily disclose & PIs can if outlined in the consent

- Does not protect against disclosure of child abuse, violence to self or others or from reporting communicable disease.

45 CFR 46.111 (8): Vulnerable Populations

a) When some or all of the subjects are likely to be **vulnerable to coercion or undue influence**, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects

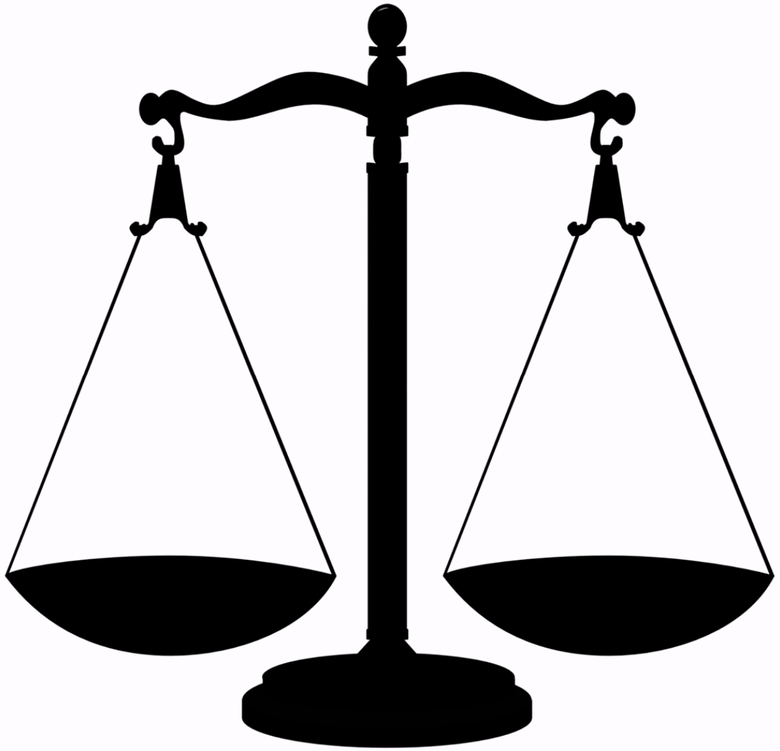
Why is this included as a criteria?

What are the consequences of not including vulnerable populations?

Good: Protected

Bad: Excluded from benefits of research

Where are the scales in either situation?



Vulnerable Subjects & 111 Criteria

- Valid Study Design: to include or not include, what are the risks?
- Subject Recruitment: easy or robust & diverse?
- Informed Consent: really informed?
- Safety Plan: does it match the risk level of the study?
- Validity of Results: will results be appropriate for all populations?
- Harms: Does this proposal results in harms to any cohort?

Section: §46.112 Review by Institution

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution.

However, those officials may not approve the research if it has not been approved by an IRB.

Section: §46.113 Suspension or Termination of IRB Approval of Research

An IRB shall have **authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.**

Any suspension or termination of approval shall include a **statement of the reasons for the IRB's action** and shall **be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.**

Section: §46.114 Cooperative Research

a) Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, **each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.**

b) (1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a **single IRB** for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision:

i. Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or

ii. Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

Summary

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