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Vulnerable populations

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Vulnerable Populations

Sarah Fowler-Dixon, PhD
Education in Human Rights Protection
May 3, 2004
Agenda

- What populations are considered vulnerable?
- What are the federal regulations associated with these populations?
- What safeguards are suggested?
History

- **World War II Germany: prisoners**
  Twin studies, effects of freezing and overheating, effects of high altitude, war wound recovery studies in concentration camps
  - Institutionalized population
    - Specifically targeted for ease of study
  - Entirely under direction of institution staff
  - Subjects influenced by desperation to make situation better
History

- Tuskegee: subjugated population
  Syphilis left untreated in impoverished black community for 40 years. Subjects were told they were receiving medication.
  - Study not explained to community at large or catered to “local research context”
  - Unjust distribution of benefits and burdens amongst racial and socioeconomic subpopulations
  - No subject autonomy: deciding according to manipulated information
  - Violation of “do no harm”
History

- Willowbrook State School, NY: cognitively impaired minors

  Institutionalized children made to ingest hepatitis contaminants. Health was monitored; no treatment was given.

  - Doubtful capacity for consent; no surrogate
  - Institutionalization taken advantage of
  - Violation of “do no harm”
  - No benefit to outweigh increased risk to minors
History

- **Lynchburg Institute, VA: “feeble-minded” and subjugated**

  Impoverished, delinquent, cognitively impaired were institutionalized and involuntarily sterilized to “improve” the human gene pool. Reinforced by Supreme Court and Virginia legislation.

  - While not a research study, still a targeting of a vulnerable population for the benefit of somebody else.
Identified Populations

- Minors
- Pregnant women, fetuses, and IVF
- Cognitively impaired
- Prisoners
- Traumatized, comatose, and terminally ill
- Elderly and aged
- Third parties
- Minorities
- International research
- Healthy volunteers
- Employees and students
The Common Thread

1. Questionable capacity to consent autonomously
2. Life situation contributing to coercion, swayed decision-making
3. Protective federal regulations
Minors

Concerns:

Consent affected by parental emotion

1. To insulate children from undue risk
2. Desperation when confronted with hopelessly ill child
3. To not treat children with procedures only researched in adults
Including Minors

From desire to prove pediatric procedures:

Correction of historical absence from studies.

Pediatric Research Equity Act (2003)

- FDA can mandate pediatric trials
  - Safety
  - Efficacy
  - Dosing and regimen

Justifications for Exclusion (45 CFR 46 Subpart D)

- It is expected that children will be included in all research involving human subjects, unless one or more of the following exclusionary circumstances can be fully justified:
Excluding Minors from Adult Studies

1. Topic is irrelevant to children.
2. Laws or regulations barring the inclusion of children in the research. (discussed next)
3. Knowledge sought in the study is already available or will be obtained
4. A separate, age-specific study in children is warranted and preferable.
5. Insufficient data are available in adults to judge potential risk in children.
6. The study is a continuation of a previous study with pre-enrolled adults.
7. Other special cases justified by the investigator and found acceptable to the review group and the Institute Director.

45 CFR 46 Subpart D
Safeguarding Minors

Consent issues:

- Minor cannot consent for themselves
- Parental motive and clarity of decisionmaking
  - Extremely upset
  - Compensation
# Risk to Minors

From desire to protect children from undue risk:

<table>
<thead>
<tr>
<th>Risk Rating</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal</strong></td>
<td>One parent’s consent</td>
</tr>
<tr>
<td>&gt; <strong>Minimal</strong></td>
<td>▪ One parent’s consent</td>
</tr>
<tr>
<td><strong>Direct benefit</strong></td>
<td>▪ Risk justified by direct benefit</td>
</tr>
<tr>
<td></td>
<td>▪ Benefit approximate to benefit from alternatives</td>
</tr>
<tr>
<td>&gt; <strong>Minimal</strong></td>
<td>▪ <strong>Both</strong> parents’ consent</td>
</tr>
<tr>
<td><strong>No</strong> direct</td>
<td>▪ <strong>Minor</strong> risk increase</td>
</tr>
<tr>
<td>benefit.</td>
<td>▪ Generalizeable knowledge</td>
</tr>
<tr>
<td></td>
<td>▪ Similar to normal life experiences</td>
</tr>
</tbody>
</table>
## Risk to Minors

<table>
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<th>Risk Rating</th>
<th>Requirements</th>
</tr>
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<tbody>
<tr>
<td><strong>Not otherwise approvable</strong></td>
<td><strong>Both</strong> parents’ consent</td>
</tr>
<tr>
<td></td>
<td><strong>Generalizeable knowledge</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Approval of DHHS</strong></td>
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</tbody>
</table>

45 CFR 46.404-407
Safeguards for Minors

- Consent process:
  - Age appropriate assent
  - Adult consent (proportional to risk)

- Research plan:
  - Expertise of the research team in dealing with children of that age
  - Appropriateness of the research facility for children
  - Statistically significant number of children are expected to enroll.

- Compensation:
  - Children: gifts only
  - Parents: Compensation for travel or time lost from work
Minor Consent
Missouri Law

MO Revised Statutes 431.061

Minors can consent for themselves if:

- Lawfully married
- Legal custodian of their or any child
- In case of:
  (a) Pregnancy, but excluding abortions;
  (b) Venereal disease;
  (c) Drug or substance abuse.
Minor Consent: Special Situations

- Accept the minor’s wishes if:
  - Adolescent declining a severely uncomfortable study, and they fatally ill

- Consider an independent consent guardian if:
  - Child abuse is evidenced
  - Transplant is being conducted between minor siblings

- Wards of the state: Conduct research only in public places where most of the children are not wards.

Pregnant Women and Fetuses

Concerns:

- Risk to the non-consenting
- Consent from all interested parties
- Poorly motivated termination of pregnancy
- Liability of sponsors and investigators for harm caused by research activities
Pregnant Women and Fetuses: Risk Concerns

45 CFR 46 Subpart B guides reviewers on the following:

1. Substantial background information about risk
   - Animal, nonpregnant women

2. If procedure poses risk to fetus …
   - Direct benefit to fetus from that procedure, OR
   - Minimal risk AND only way to obtain information
Minimal Risk for Fetuses

No greater risk than that from established procedures routinely used in an uncomplicated pregnancy or in a pregnancy with complications comparable to those in study.

Inclusion of Pregnant and Nursing Women

Inadvertent inclusion in a study including women of childbearing potential

- Provide statement of possible risk to subject or embryo, if subject is or becomes pregnant
- IRBs judge if participation poses risk to fetus or nursing infant. If so:
  - Advise nonpregnant subjects to avoid pregnancy or nursing during or following the research
  - Advise nonpregnant subjects to notify the investigator immediately should they become pregnant
  - Exclude or study separately

OHRP: IRB Guidebook. 1993
Inclusion of Pregnant and Nursing Women

Research directed at maternal health:

- Maternal needs take precedence over fetal needs, except if:
  - Maternal health benefit is minimal, and fetal risk is high. [45 CFR 46.207]
- IRB review: minimized fetal risk

Inclusion of Pregnant and Nursing Women

Studies directed at pregnancy:

- Study physiological mechanisms; *not* directed at maternal or fetal health
- Minimized fetal risk

IRBs are responsible for deciding if the study is directed at maternal health, fetal health, or pregnancy itself.

Pregnant Women and Fetuses: Consent Regulations

45 CFR 46 Subpart B

- Maternal consent
  - Direct benefit to her, OR her and fetus;
  - No benefit to her or fetus, but risk is minimized and study is the only way to gain information.
  - If a minor, can consent for self (emancipated because pregnant)

- Paternal consent
  - Direct benefit only to fetus
  - Unless unavailable, incompetent, mentally incapacitated, or guilty of rape/incest

- Informed of all possible impact on fetus
Termination within a Study

45 CFR 46 Subpart B

- The study can provide *no* inducement to terminate
- Study team may *not* participate in or advise termination
- Study team may *not* determine neonate viability
Pregnant Women and Fetuses: Safeguards

- Waiting Period
- Repeated Reconsentning
  - Single sheet summaries of key elements
Cognitively Impaired

- mental retardation/developmental delay
- dementia
- delirium
- major psychiatric disorders
- systemic illness
- other brain diseases
- some medications
Cognitively Impaired: Recent Problems

  - 3 legal advocacy groups sued on behalf of six hospitalized psychiatric patients
  - Feared existing regulations might permit investigators to enroll them in clinical research inappropriately

- **1994: OPRR investigation**
  - Suicide of a schizophrenic patient who had recently participated in a research trial at the University of California, Los Angeles (UCLA)

- **CFR: no specific protections**
  - (other than surrogacy)
Goal for Cognitively Impaired

- understand the nature of the research
- understand participation
- appreciate the consequences of participation
- consider alternatives
- make a reasoned choice
- feel free from coercive pressure of institutionalized lifestyle
Cognitively Impaired

**Question:** Does the disorder or impairment affect ability to achieve consent goals?

*Not always.*
Assessment of Understanding

- individualized
- open-ended
- elements presented individually
- oral and written
- 4th to 6th grade

On HSC website.
Cognitively Impaired: Consent Safeguards

- Conduct research only if related to impairment
- Early identification of surrogate
- Consent with surrogate’s “duplicate” consent, OR assent with surrogate’s consent
- Reconsenting
  - more critical in higher risk protocols
- Advance Directive
  - In time of competency
Surrogate Decision-making: Missouri Law

Missouri Revised Statutes 431.064 gives order of surrogacy:

1. Spouse unless the patient has no spouse, or is separated, or the spouse is physically or mentally incapable of giving consent, or the spouse's whereabouts is unknown or the spouse is overseas;

2. Adult child;

3. Parent;

4. Brother or sister;

5. Relative by blood or marriage.
Cognitive Impairment

References

- 21 CFR 50
- 45 CFR 46.109, 111, and 116
- "Informed Consent," Clinical Trials Advisor, Vol. 6, No. 18, October 11, 2001
Prisoners

45 CFR part 46.303(c)

"any individual involuntarily confined or detained in a penal institution."

- sentenced under a criminal or civil statute
- detained in alternatives to criminal prosecution or incarceration in a penal institution
- detained pending arraignment, trial, or sentencing
Prisoners

Concerns:

- Coercive environment
- Perceived ability to improve environment through study participation
- Risk of loss of confidentiality of participation, of data
  - Prisoner movement
  - Records

Included if were prisoners at time of enrollment or entered prison after enrollment.
Prisoner Protocols: IRB Committee Requirements

- Majority shall have no affiliation to prison(s) involved
- One member shall be a prisoner or appropriate prisoner representative
Permissible Prisoner Protocols

45 CFR 46.306(a)(2)

1. possible causes, effects, and processes of incarceration, and of criminal behavior
   - No more than minimal risk and inconvenience
2. prisons as institutional structures or of prisoners as incarcerated persons
   - No more than minimal risk and inconvenience
3. conditions particularly affecting prisoners
   - Hepatitis, AIDS
   - Social and psychological problems
   - Federal consultation
4. intent and reasonable probability of direct subject benefit
   - Non-beneficial control arms: federal consultation.
Prisoner Safeguards

45 CFR 46.305(a)

Benefits: not coercive

Risks: would be accepted by nonprisoner volunteers

Subject selection: random from eligible pool

- Fair to all prisoners
- No arbitrary intervention by prison authorities or prisoners

Consent:

- Understandable language
- Participation not included in parole deliberation
- Follow-up procedure accounts for varying length of sentences
Severely Ill

Includes: Traumatized, comatose, ICU patients, dying

Concerns:

- Ability to consent hampered
  - Strong painkillers
  - Unconsciousness or delirium
  - Limited time for consenting or contacting surrogates

- Coercive feeling of desperation

- Designation of surrogate
  - Same MO laws apply as for cognitive impairment
Emergency Consent of the Traumatized

Exception from informed consent permitted when:

1. situation is **life threatening**, and necessitates the use of the test article;

2. informed consent **cannot be obtained** because of an inability to communicate with, or obtain legally effective consent;

3. there is **not sufficient time** to obtain consent from the subject's legally authorized representative; **and**

4. there is **no alternative method** of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject available.
5. **Study** may be of **direct benefit** to participant.

6. **Notice** of involvement and follow-up information to patient and family will be provided as soon as possible.

7. **Community involvement.**

HSC Guideline for Emergency Research
2001 study: quality of informed consent

- Competence not always measured
  - In majority of cases, ability to consent was inferred from dementia, delirium noted in medical chart

Allan S. Brett, MD; Jason C. Rosenberg, MD. The Adequacy of Informed Consent for Placement of Gastrostomy Tubes *Arch Intern Med.* 2001;161:745-748.

It is obviously preferable for the investigative team to assess competency for consent.

*(HSC Assessment for Understanding)*
Safeguards for the Severely Ill

- Advance Directive
  - During time of lucidity
- Early designation of surrogate
- Independent monitor
  - Documentation: consent process, lucidity cycles
  - Progress of research
- Physician not act as PI
- Readily available emergency services
Considerations for Protocols Including the Severely Ill

- anticipated toxicity of the therapeutic interventions;
- extent to which subjects are likely to be debilitated by either their illness or their therapy;
- the remaining life expectancy of the subjects;
- whether participation in the research would require a change in residence (e.g., from home or hospice to a hospital or research institution).
Elderly and Aged

Concerns:
- cognitive impairment
- institutionalization
- Consenting with hearing or vision problems
Safeguards for the Elderly and Aged

- If institutionalized: Avoid this population unless research is on institutionalization.
- Consent forms in larger font
- Assessment of understanding

In general, see safeguards for cognitively impaired and prisoners.
Third Parties

Definition:

- Private, identifiable information is obtained
- Usually in scenario of interviewing family members
Third Parties

Concerns:

- Third party will feel coerced to participate by their family member’s participation being linked to their own
- Information released without third party’s consent
  - Private
  - Identifiable
Consenting Third Parties

Initial contact should always be made by the primary subject.

- **Letter to primary subject:**
  - Explanation of research and the role of the family member in the study
  - Description of information to be obtained
  - Card with self-addressed, stamped envelope so family member can grant permission
  - **NOT** acceptable for PI to obtain names/addresses of family members in order to contact them for consent to participate.
Consenting Third Parties

Waiver of consent: *(45 CFR 46.117 (d) (1-4))*

- no more than minimal risk;
- the waiver will not adversely affect subjects’ rights and welfare;
- the research could not practically be carried out without the waiver; *and*
- whenever appropriate, subjects will be provided with follow-up information
Healthy Volunteers

Concerns:

- Motive for participation
  - Altruism??
  - Compensation
- Personal risk/benefit ratio
  - “Do Not Harm”
  - Maximize benefit, minimize harm
Safeguards for Healthy Volunteers

**Compensation:** Not coercive

**Participant pool:**
1. participants with a permanent address
2. participants with a source of income
3. independent monitor
4. ask potential subjects about previous clinical trial experience (avoid enrollment of “career participants”)
   - Particularly important for very uncomfortable or dangerous studies
Employees and Students

Concerns:

- Desire to please
- Relationship to investigative team
- Security
- Frequent target of recruitment
- Confidentiality
Employees and Students: Safeguards

Recruitment:

- Avoid involvement of personal relationship.
  - general announcements or advertisements, rather than individual solicitations
- Avoid involvement of professional ambition.
  - If study participation is offered for class credit, other options should be given
    - Research paper (ungraded)
    - Attendance at faculty colloquia (merely show up)
  - If students do choose to participate in studies, they should be given several studies from which to choose.
Employees and Students: Confidentiality

Working within research environment: increased risk of disclosure

- **Safeguards:**
  - Limiting identifying information
  - Codes or encryption
  - Limited access to information
  - Information kept only for a specific length of time
  - Staff statement of confidentiality
Minorities

Based on statistical alignment of minority status with lower socioeconomic status …

Concerns:

- Under representation by recruitment through health care insurers
- Under representation due to difficulty of recruitment
- Coercion through monetary compensation
- Literacy, cultural norms, and informed consent
- Paternalism and stereotyping
Safeguards for Minorities

- Thinking outside the box for recruitment
  - Through community centers, rather than health care providers
- Provision of child care and transportation
- Consent documents adjusted for language barriers and cultural norms

Summary

- “vulnerable population”: life circumstance contributing to coercion or inability to consent

- Safeguards: prolonged or reinforced informed consent, protected confidentiality
  - HSC guidance (www.medicine.wustl.edu/hsc)
  - Federal regulations
    - 45 CFR 46, Subparts A-D
    - OHRP IRB Guidebook, Chapter 6
Final Recommendations

Anyone can be “vulnerable”, if a life experience causes their consenting ability for a given study to be minimized.

Always consider possible safeguards.