Protecting Vulnerable Subjects
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Presented by:
Rob Romanchuk, BSHS, CIP, CCRC, CCHS, CCRCP
IRB Member
About Schulman Associates IRB

- Established in 1983
- US and Canadian boards fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP)
- Superior audit history with FDA—five consecutive audits with no findings.
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
About Schulman Associates IRB

- Full board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
- **Phase I Board** with streamlined processes tailored to Phase I timelines
- **Oncology Review Board** for all phases of oncology research
- Customized services for **institutions and AMCs**
- Experienced primary points of contact for sponsors, CROs, institutions and sites
About Schulman Associates IRB

- Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

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Provision is a joint venture between Schulman Associates IRB and Falcon Consulting Group
About Today’s Presenters

Rob Romanchuk, BSHS, CIP, CCRC, CHRC, CCRCP
IRB Member

- BSHS, Clinical Research Administration, The George Washington University
- Extensive experience in IRB and research operations, HSP and GCP auditing and training
- ACRP NC Sub-Chapter chair, Winston-Salem, NC
- Frequent presenter at ACRP, MAGI and other venues
Objectives

- Identify the vulnerable in the history of human research protections
- Review the ethical constructs identifying the vulnerable
- Review current regulation and guidance governing protections for the vulnerable
  - Focus on regulatory gaps
- Construct a working model to assist in identifying and protecting vulnerable subjects for daily use
- Test this working model with mock scenarios for discussion
Current Landscape

Sample of 18 Well-Known Independent and Local IRBs

- Examined initial submission application form
  - List of vulnerable subjects varied from 0 to 38 categories
  - Most common listings:
    - Children/Minors – 18
    - Pregnant women – 17
    - Non-English speaking – 16
    - Prisoners – 13
    - Economically Disadvantaged – 12
    - Employees – 11
Findings (cont.)

- Educationally disadvantaged – 10
- Students – 9
- Decisionally impaired – 8
- Fetuses – 7
- Cognitively impaired – 6
- “Other” – 5
Current Landscape

Outliers (less than 5):
- Family members of employees
- Employees of sponsor
- Frail, elderly
- Mentally ill
- Wards of the state
- Homeless
- Traumatized/comatose
- Illiterate
- Hearing/visually impaired

- Non-US citizens
- Military personnel
- Cancer
- Terminally ill
- High risk for incarceration
- Abortuses
- Subordinates
What Is Vulnerable?

➢ Vulnerable:
  • From Latin *vulnus* (wound)
  • Indicates susceptibility to injury or attack

➢ In research:
  • Indicates greater likelihood of being misled or manipulated
  • *Merriam-Webster's New Collegiate Dictionary*:
    • *guinea pig* noun: a subject of research, experimentation or testing
History Identifies the Vulnerable

- Nazi Medical Experiments – 1932-1945
- Shiro Ishii; Manchuria – 1936-1945
- Tuskegee Syphilis study – 1932-1972
- The Thalidomide Tragedy – 1956-1962
- Willowbrook Experiments – 1954-1960
- Human Radiation Experiments – 1940s to 1970s
- Holmesburg Prison, Philadelphia, PA – Mid-1950s to 1970s
The Vulnerable Codified

- **The Nuremberg Code - 1947**
  - “The voluntary consent of the human subject is absolutely essential. (Person) should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion.”

- **The Belmont Report - 1978**
  - Refers to: “Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized”
  - Cautions against selecting populations “already burdened” by “infirmities and environments,” especially when the research imposes risks with no therapeutic intent
Belmont Principals & Vulnerability

- Respect for Persons
  - Requires that researchers treat potential subjects as autonomous individuals, free to make “considered judgments” by entering into research voluntarily and with adequate information.
  - Those with diminished autonomy require protection.
    - Factors that restrict or diminish autonomy are listed as “illness, mental disability, or circumstances that severely restrict liberty.”

- Justice – focus on equal distribution of risks and benefits
  - Prohibits the selection of subjects “simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied.”
Principles of the Belmont Report were incorporated into U.S. Federal Regulations
- 21 CFR 56.107 and 21 CFR 56.111
- 45 CFR 46.107 and 45 CFR 46.111

Vulnerability is NOT defined but regulations include:
- “...vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons”
- “... or economically or educationally disadvantaged persons”
Regulatory Construct

- 45 CFR 46 subpart B
  - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

- Subpart C
  - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

- Subpart D
  - Additional Protections for Children Involved as Subjects in Research
ICH 16.1; Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.
ICH 16.1: Vulnerable Subjects

➢ Other vulnerable subjects include:
  • Patients with incurable diseases
  • Persons in nursing homes
  • Unemployed or impoverished persons
  • Patients in emergency situations
  • Ethnic minority groups
  • Homeless persons
  • Nomads, refugees, minors
  • Those incapable of giving consent

➢ Such as:
  • Medical, pharmacy, dental, and nursing students
  • Subordinate hospital and laboratory personnel
  • Employees of the pharmaceutical industry
  • Members of the armed forces
  • Persons kept in detention
Regulatory Specifics
Added Protections: Pregnant Women & Fetuses (45 CFR 46 subpart B)

Permitted only if:

- Preclinical testing has been done on animals and non-pregnant women
- Prospect of benefit
- If no prospect of benefit – no greater than minimal risk and information cannot be gained any other way
- Consent from the mother is obtained
- Fully informed consent from both parents if fetus alone accrues benefit
- No inducements present to end the pregnancy
- No one involved in the research may have any part in timing, method or procedure to end pregnancy
- No one involved may have part in determining the viability of a neonate
Added Protections: Prisoners (45 CFR 46 subpart C)

Permissible only if:

• Research must be specific to prisoners or prisons
• Must represent no more than minimal risk

AND

IRB must assure that:

• Subject selection is fair
• Risks are commensurate with risk acceptable to non-prisoners
• No coercive advantages are offered
# Added Protections: Children (45 CFR 46 subpart D)

<table>
<thead>
<tr>
<th>Section</th>
<th>Risk</th>
<th>Benefit</th>
<th>Protections</th>
</tr>
</thead>
<tbody>
<tr>
<td>404 50.51</td>
<td>No greater than minimal</td>
<td></td>
<td>Assent/permission (at least one parent)</td>
</tr>
<tr>
<td>405 50.52</td>
<td>Greater than minimal</td>
<td>Prospect of benefit</td>
<td>Must justify risk, Show risk commensurate with alternatives, Assent/permission (at least one parent)</td>
</tr>
<tr>
<td>406 50.53</td>
<td>Greater than minimal (minor increase)</td>
<td>No prospect of benefit</td>
<td>Must provide generalizable knowledge which is of vital importance to subject or condition, Assent/permission (both parents)</td>
</tr>
<tr>
<td>407 50.54</td>
<td>Greater than minimal</td>
<td>No prospect of benefit</td>
<td>IRB must concur and Secretary must determine that represents an effort to understand, prevent or alleviate a serious problem affecting children, Assent/permission (both parents), “Sound ethical principles” applied</td>
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Regulatory Gaps

- 45 CFR 46:111(b)
  When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as 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 are included in “such as”?
  - List of vulnerable subjects has exploded – how can they be accommodated?
  - What “additional safeguards” are appropriate?
3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

- 3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

- What constitutes “special attention”? 
What About “Others”? 

- Vulnerability = diminished autonomy resulting from:
  - Diminished capacity, e.g. children
  - Limited voluntariness, e.g. prisoners

- The list of those with diminished autonomy is long

- “Added protections” for these are not defined, but are mandated

- Bioethical and regulatory concepts can be extrapolated to provide such protections
Filling the Gaps with Regulatory and Bioethical Concepts

- Consent/Assent/Permission
- Minimal Risk
- Types of Harm
- Types of Vulnerability
Valid Consent

- **Informed**
  - Principal behind “required elements” of informed consent form regulations
    - “Reasonable person” standard

- **Voluntary**
  - Free of “force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion”

- **Competent**
  - Demonstrating capacity to understand, communicate, reason and deliberate
  - Reflects decision-making capacity (DMC)
Regulatory Concepts

**Assent:** to agree, concur
- Age of assent dictated by IRB
  - Many follow “rule of 7’s”
    - 0-7 not capable of assent
    - 7-14 may provide assent
    - 14 and older may provide consent
  - Many states have their own regulations
  - May be written or oral script with documentation

**Consent:** permission, approval — by competent, fully informed legal adult, or emancipated minor

**Permission:** authorization
- Children and others with DDMC can assent, but cannot consent
- Parents or guardians may provide permission for those in their care but not consent for them
“Minimal Risk”

- The probability of harm or discomfort anticipated not greater than that encountered in daily life or during the performance of routine physical or psychological testing
  - Uniform standard – daily life of healthy child
  - Relative standard – daily life of child with disease/disorder under study
- Current application favors “uniform standard”
Bioethical Concepts: Harm

1. Physical harm: injury, illness, pain, suffering, discomfort
2. Psychological harm: anger, guilt, distress, embarrassment, anxiety
3. Social harm: ostracism, loss of rights, social standing
4. Economic harm: financial burden, higher cost, lost wages
5. Legal harms: lawsuits, arrest, conviction or incarceration
6. Dignitary harms: loss of respect, value, objectification
Types of Vulnerability

**Institutional**: those having the cognitive capacity to provide informed consent, yet are subject to the formal authority of others who may not have their individual interests at heart

- Prisoners, military conscripts, employees, students
  - Exacerbated when enrollment is incentivized, i.e. early release/parole, higher grades, promotions
  - Diminished by institutional mechanisms to preclude retaliation for refusal to enroll or early ending of participation
**Types of Vulnerability**

- **Deferential**: informal power relationships in which the potential subject defers to the will of others. Influence is more subtle than institutional (formal) relationships.
  - Elderly deference to adult children, patient deference to trusted physician
  - Mitigated by excluding the deferential party from the consent process or use of subject advocates
Types of Vulnerability

**Medical:** those who are seriously ill and drawn to research because no other satisfactory treatment seems available

- Chief component of “therapeutic misconception”
  - Cancer patient desperate for hope
  - Patient who implicitly trusts primary care physician

- Mitigated by:
  - Careful discussion of risks vs. benefits
  - Education of subject regarding changing role (from physician to investigator) or use of third party
Economic: occurs when a person is subject to “distributional disadvantage” in the form of less than adequate income, housing or healthcare

- Exacerbated by unjustified stipends, monetary inducements, free medications
- Diminished by careful consideration of monetary inducements by IRB and assuring that subject understands both risks and benefits
Types of Vulnerability

**Social:** present when the subject has the capacity to consent, but is a member of an “undervalued social group,” and describes the perception, stereotyping, and resultant discrimination placed upon this group

- Exemplified by the Tuskegee Syphilis study
- Diminished by:
  - Application of distributive justice: population that benefits should bear equal risks
  - Allowing research to specific group only if research question is relevant to the group
  - Allowing members of group to provide input in study design
  - Assuring representatives of that group are present on reviewing IRB
Bioethical Concepts: Types of Vulnerability

➢ **Cognitive or Communicative**: individuals who are unable to comprehend, deliberate and make decisions because of:

- **Limited capacity**: limited cognitive ability due to age (children) or impairment
- **Situation**: capacity exists, circumstances permit free/full use, i.e. emergency research
- **Communication barriers**: capacity present but diminished by language barriers or literacy

➢ Addressed by use of education, honor for circumstances, translation/interpretation
Non English-Speaking Subjects

- Section V.B. To prepare for unexpected enrollment of non-English speaking populations, the agency recommends that arrangements are made for “translation of a generic short form in multiple languages” (21 CFR 50.27[b][2]) to be used with the following steps:
1. The investigator consults with IRB chair (or delegate) confirm that there is no time to get a translated long form and that circumstances are correct (interpreter and translated short form available).

2. Investigator may use the translated short form and to conduct oral consent discussion with interpreter who may also serve as witness. The English long form may serve as
   a. Subject signs translated short form and is give copy along with English long form.
   b. Witness signs both short form and copy of long form
   c. Person obtaining consent signs the copy of long form.

3. If IRB chair (or delegate) was not contacted, do so promptly. In FDA regulated research, investigator obtains a translated long form ASAP and supplies to the subject.
“Capacity” includes ability:
- to make and express a choice,
- to understand relevant information,
- to appreciate the significance of the information relative to their own situation and
- to reason with this relevant information in making decisions

DDMC includes anyone judged:
- Incapable of giving informed consent
- Lacking sufficient understanding to qualify as valid informed consent
  - Possible examples: dementia, delirium, psychosis, depression, mania, intoxication, intellectual disability

*Rosenstein, Miller 2008
DDMC - Approach

➢ Do not assume consent is not possible
  • DMC is variable even within groups
  • DMC can improve with education
  • Level of DMC may change through the course of the study
  • Follow IRB’s direction
  • May defer to investigator

➢ Even when consent is not possible – assent may be

➢ Follow IRB direction and state law in use of surrogate consent
FDA Draft Guidance: DDMC

- If enrollment of these populations is ethically appropriate and scientifically necessary, additional safeguards may include:
  
  • Use of an independent “qualified professional” to assess the consent capacity of potential subjects at the time of consent and in an ongoing manner
  
  • Establish a waiting period to allow additional time for decision making
  
  • Use of methods to enhance consent capacity; e.g., repetition, simplification, enlisting a subject advocate or trusted family members
Additional safeguards (cont.):

- Use of questionnaires to assess understanding
- Re-assessment for progressive disorders
- Involving LARs as cognition declines
- Including assent mechanism
- IRB or third party observation
Scenario 1

A research coordinator is called to assist in the consent process involving a 62 year old female who has just learned that her breast cancer has recurred. As the coordinator enters the room, the patient is present along with 2 adult daughters. After a short introduction, it appears as though her cognitive abilities are fully intact. When the coordinator begins speaking, the woman looks helplessly at her daughters.
This patient displays deferential vulnerability. What can the coordinator do to mitigate these influences? (all that apply)

A. Ask the daughter to leave the room
B. Kindly bring to light the mother’s deferential leaning and encourage discussion
C. Ask the daughter to act as LAR
D. Schedule a consent session for another day and encourage interim discussion with family and caregivers
Scenario II

An academic investigator is conducting a study that requires healthy adults. The project is underfunded. To assist, one of his student interns steps forward to volunteer as a subject.
This student is subject to institutional vulnerability. What can be done to minimize it? (all that apply)

A. Have someone other than the PI conduct consent

B. Have the PI promise that there’s no pressure and grades won’t be effected

C. Insert language in IC to assure non-coercion

D. Thank her and decline her offer
Putting It Together

Scenario III

An investigator is considering the enrollment of a patient with acute chest pain in a clinical trial to assess the safety and efficacy of an investigational drug to decrease infarct size. The patient is in pain, but has received morphine with some relief. His wife is present. Both are very anxious. As the investigator explains the study the patient says:

“Whatever you say, Doc.”
Putting It Together

- This patient is subject to deferential and possibly cognitive vulnerability.

- What can be done to minimize or eliminate it? (all that apply)
  
  A. What’s the problem? Sign him up!
  B. Have someone other than the PI conduct consent
  C. Have the wife act as LAR
  D. Wait till the morphine wears off, then consent
  E. Apply the brakes, explain the difference between research and treatment, assess understanding and carefully proceed with consent
Putting It Together

➢ Scenario IV

The IRB has before it a protocol for a randomized, placebo controlled study of a novel treatment for mild cognitive impairment (MCI). Entry criteria excludes patients with diagnosed Alzheimer’s Disease. The end point is delay in conversion of MCI to AD. The study will last 3 years. The informed consent requires signatures for the subject and provides optional lines for a surrogate or LAR.
Putting It Together

- Patients recruited for this study may be potentially cognitively vulnerable.
- What can be done to accommodate this potential vulnerability? (all that apply)
  A. Assess cognitive capacity with a valid tool
  B. Augment consent process with added time, teachback methods and simplification
  C. Even in case of full cognition, identify eligible LAR and include in consent discussion
  D. Use assent when employing LAR
  E. Reassess cognition periodically during study
Summary

➢ Vulnerability is a most critical aspect of clinical research.
  • It has driven the regulations governing research
  • Honoring it give us continued permission to conduct research
  • Ignoring it brings harm and rightfully restricts research

➢ Regulations can’t cover every person or situation. So having a working mental construct to identify vulnerability in its many forms along with practical ways to mitigate its influencing factors is an essential skill for all research professionals.
  • It protects research subjects
  • It protects CRPs from serious blunders and their consequences