PROTECTING HUMAN SUBJECTS IN HIV PREVENTION RESEARCH: IRB Review

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Human Subjects Protection: Shared Responsibility

IRB
Chair, members, staff
DSMB
Sponsor
Industry, CRO, government
Research Team
PI, Co-Investigators, Staff
Regulator
DHHS, FDA, State Gov’t
Institution
Institutional officials, leadership

Summary Question

- Would you enroll your family member in this study?

Ethics and Regulations

- Ethics → what you SHOULD do
- Regulations → what you MUST do

BELMONT REPORT

3 Ethical 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
Beneficence

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

Consider All Risks

- Physical
- Psychological
  - Embarrassment
- Social
  - Stigmatization
- Economic
  - Employment risk
  - Insurability
- Legal
  - Criminal/civil liability

Justice

- Treat people fairly
- Fair sharing of burdens and benefits of research
- Not procedural justice, but distributive or social justice

The Ethical Principles

BELMONT
- Respect for Persons
- Beneficence
- Justice

MY GRANDMOTHER
- Show respect
- Do the right thing
- Be fair

Applying Research Ethics

Research Regulations

A floor---
Not a ceiling
Protection of Human Subjects in Research

The US Government and the IRB

DHHS

Food and Drug Administration

NIH

Office of Human Research Protection

Institutional Review Board

Federal Regulations and Policy

- HHS regulations
  45 CFR 46 - DHHS Policy for Protection of Human Research Subjects - Subpart A
    - originally adopted January 13, 1981
    - Revised June 18, 1991
- “The Common Rule”
  - Federal Policy for Protection of Human Subjects
    - June 18, 1991
    - Adopted by 17 federal agencies

Federal Regulations
45 CFR 46

Additional Protections
- Subpart B Pregnant women, fetuses, neonates
- Subpart C Prisoners
- Subpart D Children
- Subpart E Registration of IRBs

Food and Drug Administration

- Authority
  - Federal Food, Drug and Cosmetic Act
- Regulations
  - IRB 21 CFR 56
  - Informed Consent 21 CFR 50
  - Investigational Drugs 21 CFR 300
  - Investigational Biologics 21 CFR 600
  - Investigational Devices 21 CFR 800
  - Financial Disclosure 21 CFR 54

INSTITUTIONAL REVIEW BOARD

Purpose: To protect the rights and welfare of human subjects of research.

(help researchers conduct scientifically valid and ethically sound research)
What is an IRB?
45 CFR 46.107
21 CFR 56.107

- 5 members
- Varying backgrounds
- Sufficiently qualified
- Diversity of race, gender, culture
- Scientist and non-scientist member(s)
- Not all of same profession or institution
- Consultants as needed

BUMC IRB (2012)

- Panel Blue
- Panel Green
- Panel Purple
- Panel Orange
- Western IRB

The BUMC IRB (2011)

Panel Blue
- Neurology
- Neuroradiology
- Psychiatry
- Emergency Medicine
- Internal Medicine
- International Health
- Nursing
- Pharmacy
- Epidemiology
- OB-GYN
- Biostatistics
- Dental Public Health
- Biostatistics
- Non-science

Panel Green
- Surgery
- Pediatrics
- Infectious Disease
- Epidemiology
- Dentistry
- Oncology/Hematology
- Nursing
- Public Health
- Immunology
- Pharmacy
- Cardiology
- Biostatistics
- Non-science

Panel Purple
- Neurology
- Nursing
- Dentistry
- Life Sciences
- Non-science

Criteria for IRB approval
45 CFR 46.111
21 CFR 56.111

- Risks are minimized
- Risks are reasonable in relation to benefits
  - To subjects, if any
  - Importance of knowledge
- Selection of subjects is equitable
- Informed consent will be obtained
- Informed consent will be documented
- Safety monitoring, when appropriate
- Protection of privacy, when appropriate
- Additional safeguards for vulnerable populations

IRB DECISIONS

1. Approve
2. Conditionally Approve
3. Defer
4. Disapprove

INFORMED CONSENT

vs.

INFORMED DECISION MAKING

1. Information
2. Comprehension
3. Voluntariness
Informed Consent Process does not equal Informed Consent Form

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INFORMED CONSENT FORM
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Statement from Actual Consent Form

“You must be able to read and speak English. If you are unable to read this, you will not be eligible for the study.”
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Statement from Actual Consent Form

“The radiation to which you would be exposed is no greater than that during a nuclear attack.”
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Statement from Actual Consent Form

“Read the consent and sign it if you decide to participate. If you decide not to participate then you will be referred to the Psychiatry Walk-in Clinic.”
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Statement from Actual Consent Form

“The only risk is that participants might find the task a little boring, but no more so than any other aspect of their educational experience.”
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Protection of Human Subjects in Research

Statement from Actual Consent Form

“If you are a woman who is having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant.”

BUMC 5/03

Statement from Actual Consent Form

“We will insert 3 catheters, one in each arm.”

ARENANewsletter, 1989

Ongoing Subject Protection

- Adverse Event Review
- Protocol Amendment Review
- Protocol Deviation Review
- Progress Reports → Continuing Review
- Data Safety Monitoring (DSMP and/or DSMB)
- Audits

ACTG 076
AZT to Prevent MTCT

- Conducted in US and France
- Pilot begun in April 1991

ACTG 076--Background

1992

- AZT (ZDV) indicated for CD4 <200 (few women and no pregnant women in studies) – only first line drug FDA approved
- 90% infants infected in utero, intrapartum, post-delivery; timing uncertain
- Prevalence: 1.5 – 13 – 50/1000 in US
- Vertical transmission: 7-40% (~30%)
- Median survival: 38 months

ACTG 076 – Study Design

Pregnant women (CD4 200-500)
14-34 weeks & infants

Stratified Randomization:
14-26 weeks
>26 weeks

Evidence of definitive HIV infection in infant at week 75; f/u to 3 yo

AZT
Placebo

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**ACTG 076- Enrollment Criteria**
- HIV +, no ARVs during this pregnancy
- 14-34 wks
- Lab values
- ≥ 13 yo or "local IRB age of consent, whichever is higher"
- Intend to carry to term
- Consent
- No hx of AZT intolerance

**ACTG 076 Interventions**
- Mom: AZT 100 mg or placebo 5x daily
- L&D: AZT loading dose 2 mg/kg; continuous infusion 1 mg/kg/h or placebo until cord clamped
- Infants: AZT syrup 2 mg/kg po or placebo 4x daily or IV 1.5 mg/kg q 6 h for 6 weeks

**ACTG 076 Outcome Measure**
Definitive determination of HIV:
- One + HIV viral culture of blood or CSF
- If > 15 mo of age, 2 separate positive screening tests (ELISA, then western blot)
- "Using current HIV culture technology, a negative HIV test at 18 months is required to ensure that the infant is not infected."

**ACTG 076 – Statistical issues**
- Sample Size: 748 mother-infant pairs (636 evaluable) [15% dropout]
- 3 interim and 1 final efficacy analysis, after each 160 births are evaluable.
- ITT analysis

**ACTG 076 - Safety**
- If mom’s CD4 drops below 200, discontinue participation and treat
- DSMB will evaluate pilot of 30 mother-infant pairs for safety, feasibility, logistics
- Infants with definitive determination of HIV infection are D/Cd and followed.

**ACTG 076 Ethical and Regulatory Issues**
- Standard of care
- Mother vs. Fetus/Infant
- Consent – mother/father
- Subpart B
- Subpart D
- Confidentiality
- Is information burdensome?
- Stigma