EVIDENCE-BASED HIV PREVENTION RESEARCH ETHICS
34 million people living with HIV

In 2010

- 1.8 million people died of AIDS related illnesses
- 2.7 million people were newly infected with HIV

Adults and children estimated to be living with HIV, by WHO Region, 2010

Total: 34.0 million [31.6 million – 35.2 million]

INTERNATIONAL RESEARCH EFFORTS SCANDALIZED

- Popular culture
  - *The Constant Gardner*

- Popular media
  - *Washington Post* series: *The Body Hunters*

- Professional journals
  - *NEJM* concerning placebo-controls in the vertical transmission of HIV
Methods in bioethics

An obligation to obtain empirical evidence

Some examples

- Placebo controls
- Informed consent
THEORETICAL METHODS

- Philosophical
- Theological
- Casuistic
- Historical
- Legal
- Literary
EMPIRICAL RESEARCH IN BIOETHICS

- Defined: “the application of research methods in the social sciences (such as anthropology, epidemiology, psychology, and sociology) to the direct examination of issues in medical ethics.”
- Distinguished from other forms of ethics such as normative ethics and metaethics
EMPIRICAL METHODS

- Qualitative
  - Focus groups
  - Interviews
  - Observation
  - Documentation

- Quantitative
  - Pre-existing data bases
  - Surveys
  - Psychological instruments
  - Economic/decision science instruments
  - Other quantifiable data
  - Cross-sectional vs. prospective vs. experimental
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN MEDICAL ETHICS

- Purely descriptive studies
  - Beliefs about morality and moral behavior
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN MEDICAL ETHICS

- Purely descriptive studies
- Testing established or new norms
  -Extent to which patients’ preferences for care are honored
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
  - The effects of truth telling about diagnoses of life-threatening conditions
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
  - Historical studies in similar situations
  - Studies in other settings where there is a difference
  - Psychological studies of those likely to be affected
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
  - Utility of certain procedures such as CPR
- Empirical testing of normative theories
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
  - Degree of agreement of decisions among patients and their designated surrogate decision-makers
- Case Reports
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- **Case Reports**
  - Rich description of a difficult case
- Demonstration projects
POTENTIAL ROLES FOR EMPIRICAL RESEARCH IN BIOETHICS

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- **Demonstration projects**
  - Description of the effect of an educational intervention regarding a policy concerning advance directives
A QUARTER CENTURY OF EMPIRICAL RESEARCH IN BIOMEDICAL ETHICS

Jeremy Sugarman, Ruth Faden, and Alison Boyce
Determined the total number of postings in the entire database in each five-year interval from 1980-2005.

Identified all biomedical ethics publications for each time period, searching for “ethics” as a MeSH term.

Combined “ethics” with a search strategy designed to retrieve empirical postings.
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Total</th>
<th>All Ethics</th>
<th>Empirical Biomedical Ethics</th>
<th>Empirical Biomedical Ethics/Ethics postings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1984</td>
<td>1460276</td>
<td>7667</td>
<td>577</td>
<td>8</td>
</tr>
<tr>
<td>1985-1989</td>
<td>1809682</td>
<td>11166</td>
<td>1035</td>
<td>9</td>
</tr>
<tr>
<td>1990-1994</td>
<td>2059890</td>
<td>18315</td>
<td>2220</td>
<td>12</td>
</tr>
<tr>
<td>1995-1999</td>
<td>2281690</td>
<td>21751</td>
<td>3247</td>
<td>15</td>
</tr>
<tr>
<td>2000-2005</td>
<td>3488522</td>
<td>30196</td>
<td>4822</td>
<td>16</td>
</tr>
<tr>
<td><strong>1980-2005</strong></td>
<td><strong>11099992</strong></td>
<td><strong>89095</strong></td>
<td><strong>11776</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>
PROPORTION OF BIOMEDICAL ETHICS POSTINGS USING EMPIRICAL METHODS OVER TIME

![Graph showing the proportion of biomedical ethics postings using empirical methods over time. The x-axis represents time periods from 1980-1984 to 2000-2005, and the y-axis represents the percentage of posts using empirical methods. The graph indicates an increasing trend over time.]
METHODS OVER TIME

Methods used in empirical biomedical ethics studies

Time period:
- 1980-84
- 1985-89
- 1990-94
- 1995-99
- 2000-2005

Ratio:
- Ethnology
- Focus Groups
- Qualitative Research
- Questionnaires
- Comparative study
DISCUSSION

- The primary value of this analysis is to identify the major trends in empirical bioethics research.
- Empirical research in biomedical ethics represents 13% of the total postings in bioethics.
- The proportion of biomedical ethics literature that uses empirical research methods appears to be increasingly steadily, although the rate of increase appears to have slowed in recent years compared to the late 1980s to 1990s.
- More than a third of all the empirical studies used questionnaires. In addition, most methods were descriptive. However, other powerful research methods, such as randomized trials, were seldom used.
EMPIRICAL METHODS

- Qualitative
  - Focus groups
  - Interviews
  - Observation
  - Documentation

- Quantitative
  - Pre-existing data bases
  - Surveys
  - Psychological instruments
  - Economic/decision science instruments
  - Other quantifiable data
  - Cross-sectional vs. prospective vs. experimental
<table>
<thead>
<tr>
<th>Qualitative Research</th>
<th>Quantitative Research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General research focus</strong></td>
<td>Description, documentation, and analysis of patterns; values, worldview, meanings, beliefs, and attitudes. Totality of experiences in natural or particular contexts. Generally broad, holistic, and comprehensive; worldview.</td>
</tr>
<tr>
<td><strong>Scope</strong></td>
<td>Generally broad, holistic, and comprehensive; worldview.</td>
</tr>
<tr>
<td><strong>Research goal</strong></td>
<td>Development of understandings and meanings of what one sees, hears, experiences, and discovers through a variety of sensual observation-participation modes. Obtain a full and accurate “truth” from people.</td>
</tr>
<tr>
<td><strong>Sources of data</strong></td>
<td>Participants, informants, role takers, and respondents.</td>
</tr>
<tr>
<td><strong>Domains of analysis</strong></td>
<td>Can reformulated and expand focus of study as one proceeds. No predetermined, <em>a priori</em> judgments. Open discovery. Flexible and dynamic. Moves with people, context, situation, or events.</td>
</tr>
</tbody>
</table>
ETHNOGRAPHIC METHODS

- Multiple techniques
- “Thick” description
- Participant-observation
  - e.g. Getting Rid of Patients
- Interviews
  - Informal vs. semi-structured vs. structured
  - Key informants
- Focus groups
  - Conflicts of interest in research
  - Pregnant women’s views on UCB banking
MAJOR LIMITS OF QUALITATIVE METHODS

- Time consuming
- Bias cannot be completely excluded
- Lack generalizability
Existing databases – e.g. – linking DNR orders to cost data, mortality, place of death, diagnosis

Advantages
- BIG numbers
- High generalizability

Disadvantages
- Limited data, generally not designed for investigator’s purposes
- Sometimes too sensitive
- Validity often not established
Vast majority of empirical bioethics research

Most generalizable – national samples, over-sampling the underrepresented, appropriately weighted
SURVEY QUESTION DESIGN

- Off the shelf vs. starting fresh
- Single items vs. scales
- Translation
- Validity
  - Expert panels (face validity)
  - Cognitive pre-testing
- Reliability
- Pilot testing
- Psychological instruments
  - Anxiety, depression, cognitive capacity
  - Stress
- Decision theory and economics
  - Time-tradeoffs
  - Willingness to pay
- Biological
  - Cortisol
  - PET-scans & f-MRI
Most useful for

- Education
- Program implementation
- Testing a predicted outcome
- Qualitative & qualitative & theoretical
- Interdisciplinary research
- Thirteen Ways of Looking at a Blackbird
Clinical research is predicated on the notion that we need data to determine ‘truth’ and facilitate sound decision-making.

Ironically, methods of clinical research, including those designed to protect participants such as conclusions about appropriate trial design in particular cases and informed consent, are introduced without data regarding safety or efficacy.

Where relevant we need to evaluate these protections as we would any proposed clinical intervention.

US study 076
- The regimen
  - Oral AZT during pregnancy
  - IV AZT during labor and delivery
  - No breast feeding
- The results
  - Decreased vertical transmission to 8%

Contemporaneous trials in Africa and Asia
- Lurie and Wolf
- Angell: Tuskegee analogy
“The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”
RESEARCH DESIGN AND PLACEBOS

- **Why?**
  - Smaller sample size
  - Improved assessments of efficacy and safety

- **When?**
  - No known effective treatment
  - Others?
PLACEBO-CONTROLS IN SHORT-TERM CLINICAL TRIALS OF HYPERTENSION
THE CONTENTIOUS NATURE OF USING PLACEBO-CONTROLS IN STUDIES OF HYPERTENSION

- Challenged by Rothman and Michels
  - “despite the established efficacy of many agents in treating mild-to-moderate hypertension.”
    - Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *NEJM* 1994; 331: 394-398
- Seemingly inconsistent with the Declaration of Helsinki (October 2000, prior to December 2002 clarification)
Short-term placebo-controlled trials for mild to moderate hypertension are common, despite claims that they are ‘unethical’.

ICH would seem to permit such trials, “if withholding the effective treatment leads to no serious harm and if patients are fully informed about available therapies and the consequences of delayed treatment.”
METHODS

- Medline search, 1/97-12/98
- Inclusion criteria
  - RCTs
  - Mild to moderate hypertension
  - Non-pregnant adults
  - Placebo use
  - Trial duration <20 weeks
  - Primary data
- Articles abstracted
RESULTS

- 267 postings
- 80 met inclusion criteria
- 25 provided adequate data for abstraction
- Sample sizes 20-734
- Total sample of 6409
- Power to detect 2.5 in 1000 difference in treatment arms
<table>
<thead>
<tr>
<th>SAE</th>
<th>Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4,878</td>
<td>1,604</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CHF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>
ANALYSES

- Maximum-likelihood method
  - difference = 0, 95% CI: –0.002 to 0.0006

- Bayesian posterior analysis
  - 50th percentile for the posterior distribution of the difference = –0.0004; 95% credible set limits: –0.003 to 0.0006
Trials are of short duration
Only patients with mild or moderate disease
Patient-subjects closely monitored
LESSONS

- When medical treatments involve long-term benefits, determining whether placebo-controls are appropriate involves understanding the duration of treatment to confer such benefits – this is an empirical question.
- General edicts concerning placebo use need to be sensitive to the real risks and benefits involved.
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

http://www.wma.net/e/policy/17-c_e.html
INFORMED CONSENT

- Concerns about informed consent
- Innovative approaches to informed consent for vaginal microbicide trials
- Attitudes towards consent quizzing
Case-control study to identify host resistance factors in low and high risk HIV-negative persons

Oral exam on informed consent; passing score of 80% (12/15)
- 15 participants had a single meeting with physician: 20% passed
- 30 participants had three meetings with counselor: 80% passed

<table>
<thead>
<tr>
<th>Question</th>
<th>% Yes N=105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were you informed about the objectives?</td>
<td>94</td>
</tr>
<tr>
<td>Did you know you were free to abstain?</td>
<td>65</td>
</tr>
<tr>
<td>Did you know you were free to withdraw?</td>
<td>48</td>
</tr>
<tr>
<td>Did you get the impression participating was routine care?</td>
<td>53</td>
</tr>
<tr>
<td>Did you get the impression that the advantages of participating made it hard to say no?</td>
<td>87</td>
</tr>
</tbody>
</table>

First-time attendees being recruited for an HIV transmission study
- 56 women randomly selected for interviews
- 88% said they felt compelled to participate

A Social Science Approach to Informed Consent for a Microbicide Trial

Cynthia Woodsong, Ph.D.  
Family Health International
Informed Consent Tools

Print Materials

- Illustrated booklets
- Fact sheets
  - potential participants
  - male partners
  - community members/leaders
- Table-top flipcharts
- Frequently asked questions
The evolution of “Serena”
Informed Consent Tools

Visual aids

- Applicator tubes
- Applicator box
- Blood draw vials
- Vaginal/pelvic model
- Randomization envelope and colored paper
- Placebo props
ARE THERE ADVERSE CONSEQUENCES OF QUIZZING DURING INFORMED CONSENT FOR HIV RESEARCH?
RESEARCH TEAM

While quizzing during informed consent for research to ensure understanding has become commonplace, it is unclear whether the quizzing itself is problematic for potential participants.

There may be unique concerns among vulnerable populations who may have had limited formal education or who are otherwise unaccustomed to being quizzed.
A multinational HIV prevention research trial enrolling injection drug users in China and Thailand.
Opiate injectors recruited from community and screened

Short-Term Medication Assisted Treatment
Suboxone detox At Bx and 6 months plus one year of counseling; Referral to local resources

Long-Term Medication Assisted Treatment
12 months of Suboxone plus one year of counseling; Referral to local resources

HIV testing and counseling Every 6 months Year 02

If not eligible, referred to local resources
METHODS

- Enrollment procedures included an informed consent comprehension quiz
- An informed consent survey (ICS) followed
Informed Consent for Enrollment Evaluation Survey

Staff administering survey: __________________________

Instructions: I would like to ask you questions about how you felt when you took the comprehension quiz earlier today. Unlike before, there are no correct or incorrect answers to the questions I am going to ask you. Please know that your answers to this survey do not affect your participation in the trial. We are asking you these questions only because we want to know how it felt to be asked questions about the trial after the informed consent process.

1. Would that be OK? ............................................. [ ] yes [ ] no. If no, end of form.

To begin, I am going to ask you six questions about how you felt when taking the comprehension quiz. After each question, please tell me if you felt that way or not. You can respond by saying that you strongly disagree, disagree, neither disagree or agree, agree, or strongly agree with the statement.

2. When taking the comprehension quiz:
   
   2a. you were anxious ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree
   
   2b. you did not mind ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree
   
   2c. you were bored ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree
   
   2d. you were irritated ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree
   
   2e. you found the questions easy ......................... [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree
   
   2f. you felt pressured ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree

Instructions: I am now going to ask you two more questions. The responses are the same as before.

3. Taking the comprehension quiz made you feel like the researchers really wanted you to understand the clinical trial: ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree

4. Testing is a good way to find out if a person really understands the clinical trial: ............................................. [ ] strongly disagree [ ] disagree [ ] neither disagree or agree [ ] agree [ ] strongly agree
525 participants completed the ICS
- Heng County, China=255
- Xinjiang, China=229
- Chiang Mai, Thailand=41

Mean age = 33
Mean educational level = 8 yrs
<table>
<thead>
<tr>
<th>Informed consent evaluation survey Questions for participants</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were anxious</td>
<td>28/525 (5%)</td>
<td>41/525 (8%)</td>
<td>456/525 (87%)</td>
</tr>
<tr>
<td>Did not mind</td>
<td>446/525 (85%)</td>
<td>55/525 (10%)</td>
<td>24/525 (5%)</td>
</tr>
<tr>
<td>Were irritated</td>
<td>28/525 (5%)</td>
<td>14/525 (3%)</td>
<td>483/525 (92%)</td>
</tr>
<tr>
<td>Found questions easy</td>
<td>5/525 (1%)</td>
<td>7/525 (1%)</td>
<td>513/525 (98%)</td>
</tr>
<tr>
<td>Felt pressured</td>
<td>358/525 (68%)</td>
<td>98/525 (19%)</td>
<td>69/525 (13%)</td>
</tr>
<tr>
<td>Felt that quizzing indicated that the researchers really wanted them to understand the clinical trial</td>
<td>29/524 (6%)</td>
<td>72/524 (14%)</td>
<td>423/524 (81%)</td>
</tr>
<tr>
<td>Felt testing is a good way to find out if a person really understands the clinical trial</td>
<td>520/525 (99%)</td>
<td>4/525 (1%)</td>
<td>1/525 (&lt;1%)</td>
</tr>
</tbody>
</table>
Lower educational level was associated with not minding the quizzing (6-10 yrs versus 0-5 yrs: OR=0.27, p=0.03; more than 11 yrs versus 0-5 yrs: OR=0.18, p=0.03).

Site differences (Heng County versus Xinjiang) were associated with:

- feeling anxious (OR=0.07; p=<0.01)
- not minding (OR=0.26; p=0.03)
- being bored (OR=0.25; p =0.01)
- not finding the questions easy (OR=0.10; p=<0.01).
<table>
<thead>
<tr>
<th>Question</th>
<th>Score Mean</th>
<th>Score STD</th>
<th>After rotation Factor 1 loading</th>
<th>After rotation Factor 2 loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were anxious</td>
<td>0.90</td>
<td>0.64</td>
<td>0.75</td>
<td>-0.07</td>
</tr>
<tr>
<td>Were bored</td>
<td>0.99</td>
<td>0.62</td>
<td>0.81</td>
<td>0.02</td>
</tr>
<tr>
<td>Were irritated</td>
<td>1.17</td>
<td>0.51</td>
<td>0.76</td>
<td>0.02</td>
</tr>
<tr>
<td>Felt pressured</td>
<td>0.81</td>
<td>0.63</td>
<td>0.57</td>
<td>0.24</td>
</tr>
<tr>
<td>Did not mind</td>
<td>0.83</td>
<td>0.63</td>
<td>0.12</td>
<td>0.32</td>
</tr>
<tr>
<td>Found questions easy</td>
<td>0.59</td>
<td>0.75</td>
<td>0.18</td>
<td>0.35</td>
</tr>
<tr>
<td>Felt researchers really wanted them to</td>
<td>1.09</td>
<td>0.33</td>
<td>-0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>understand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felt testing is a good way to find out if a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>person really understands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance explained by each factor (%)</td>
<td></td>
<td></td>
<td>27.14</td>
<td>22.86</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- While overall, quizzing during the informed consent process is acceptable to most participants, it can be problematic for a minority of them.
- These problems may be associated with the setting in which research takes place and educational level.
UNANSWERED QUESTIONS

- What constitutes adequate understanding?
- What aspects of the study are important to understand?
Introduce empirical findings into conceptual and policy discussions as well as research ethics review.

Develop a research agenda for future work based upon the relevant conceptual and policy questions.