Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

Introduction

• 10/90 Gap
• 2011: Clintrials.gov – overseas > domestic
• Global Health
• Funding from BMGF, PEPFAR, Wellcome Trust, Fogarty, others
• Drug companies: great interest

• Spoiler: issues in international research are the same as domestic, only magnified and with some twists and turns
Introduction
What do US IRB members fear?

• Study of US IRBs and issues of international research
  – Lack of local knowledge
  – Standard of care
  – Different views of autonomy
  – Different risks and benefits of daily life
  – Corruption
  – Sustainability
  – Compensation

Outline of Presentation

• The hierarchy of norms
  – From Aristotle to Cicero

• Clinical research in low resource countries
  – Issues
  – Exploitation
  – Benchmarks

• The standard of care debate
Hierarchy of Norms

- Moral Theory
- Principles
- Codes
- Reports
- Guidelines
- Conferences
- Regulations and Laws
- Sponsor Standards
- Institutional Standards
- Standard Operating Procedures

- Universal
- Specific

- Ethical
- Practical
Principles

• **Nuremberg Code 1949**
  - Emphasis on individual, informed, voluntary, legal consent without fraud, deceit, duress
  - Minimizing risks, risks justified relative to benefits, never cause deliberate harm
  - Prepared to terminate study when necessary

• **Declaration of Helsinki 1964 plus revisions**
  - World Medical Association
  - Expanded and includes vulnerable and legally authorized representatives, assent
  - Duty to protect the life, health, privacy, and dignity of subjects
  - Privacy, confidentiality, oversight, etc.

• **Belmont Report 1979**
  - Respect for Persons- Autonomy
  - Beneficence/Nonmaleficence
  - Justice
International Codes

CIOMS

• Council for International Organizations of Medical Sciences
    – “The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care.”
Research in Developing Countries
Some Controversies

• Issues/controversies in recent years
  – Standard of care
  – Reasonable availability
  – Quality of informed consent

*What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research.* Emanuel et al JID 2004:189;930-7
Research in Developing Countries

Exploitation

• **Minimize exploitation**
  – Important for all ethical frameworks
  – Definition: Unfair level of benefits or unfair burden of risk
  – Why not as high a risk of exploitation in developed countries?
    • Society funds research to improve health
    • Researchers and research institutions are part of the community
    • There is an infrastructure that translates research to practices- thereby benefiting the community

*What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research*. Emanuel et al JID 2004:189;930-7
Clinical Research in Developing Countries

Exploitation

• Why is there an increased risk for exploitation in developing countries?
  – Poor
  – Limited health care services
  – Illiteracy
  – Cultural and linguistic differences
  – Limited understanding of nature of scientific research
  – Regulatory oversight less developed and poorly funded

• These are not sufficient or necessary for exploitation, but increase possibility.

• Issue of “neo-colonialism”

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What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research

Emanuel et al JID 2004:189;930-7

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair Selection of Study Population
5. Favorable Risk-Benefit Ratio
6. Independent Review
7. Informed Consent
8. Respect for Participants and Communities
1. Collaborative Partnership

- Decreases exploitation
- Country decides if research is responsive
- Improves lasting impact
- Mutual respect for cultural differences
- Shared responsibility
- Aspires to minimize disparities — at least those related to the project
- Fair distribution of rewards of research
2. Social Value

- Specify beneficiaries of research
  - “cui bono?”
- Importance of the health problems
- Enhance social value through
  - dissemination of knowledge,
  - product development,
  - long term research collaboration,
  - health systems improvements
- Do not supplant the extant health system
3. Scientific Validity

- Design provides social value for beneficiaries of research
- Design meets objectives while allowing participants to get usual health care
- Study is feasible within local context or with sustainable improvements
4. Fair selection of study population

• Select sample to ensure scientific validity
  – e.g., high prevalence
• Select sample to minimize risk and maximize collaborative partnerships and social value
• Identify and protect vulnerable populations
  – Consider marginalized, politically powerless, economically disadvantaged within local context

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research
Emanuel et al. JID 2004;189:930-7
5. Favorable risk-benefit ratio

• Assess risks and benefits in the context of the sample’s health risks

• Assess net risks with net benefits
  – including collaborative partnership, social value, respect for study populations

• Use of placebos

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research
Emanuel et al JID 2004:189;930-7
6. Independent review

- Public accountability through reviews mandated by regulations
  - Special need for transparency
- Public accountability through reviews by internationals/NGOs as appropriate
  - How to adjudicate discrepancies between IRBs
- Reviews are independent and competent

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research
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7. Informed consent

- Involve community in recruitment and incentives
- Disclosure and consent: culturally and linguistically appropriate
- Supplementary community and familial consent, if appropriate (spheres of consent)
  - Permission for individual consent, not true consent
- Ensure freedom to refuse or withdraw
Is informed consent worse in developing countries?

• Article analyzing studies of consent comprehension
• Wide variation across studies and mostly little difference between developed and developing:
  – Overall both understood purpose, risks, other study details
  – Both poorly understood randomization and design
  – Developing country participants scored more poorly on voluntariness and withdrawal

8. Respect for persons and communities

• Protect confidentiality

• Provide new information after study starts

• Evaluate for medical conditions and develop interventions at least as good as local norms
  – Cannot undo health care infrastructure deficiencies
  – Can determine with local partners a reasonable approach

• Inform participants and study community of results
The Standard of Care Debate...

Theoretical Continuum of Standards

- US de jure
- US de facto
- WHO de jure
- Uganda de jure
- Uganda best de facto
- Uganda local de facto
<table>
<thead>
<tr>
<th>Organisation</th>
<th>Valid science</th>
<th>Social benefits to host country</th>
<th>Favourable individual risk:benefit ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNAIDS(^{10})</td>
<td>The research protocol should be scientifically appropriate</td>
<td>Plans should start during initial stages of vaccine development to ensure availability</td>
<td>The minimum should be to provide the highest level of care attainable in the host country</td>
</tr>
<tr>
<td>NBAC(^{8})</td>
<td>There needs to be a justification for the alternative trial design</td>
<td>An explanation of how interventions proven to be effective from the research will become available to the host country population</td>
<td>Ethics committee needs to assess the risks to the participants</td>
</tr>
<tr>
<td>CIOMS(^{6})</td>
<td>Established effective intervention would not yield scientifically reliable results</td>
<td>Trial should be responsive to the health needs of the trial population and there should be assurance of reasonable availability</td>
<td>Potential risks and benefits are reasonably balanced and risks are minimised</td>
</tr>
<tr>
<td>EGE(^{7})</td>
<td>Research methods are necessary to the aims pursued and that no alternative more acceptable methods are available</td>
<td>Justification may be to simplify or reduce costs of treatment for host country</td>
<td>Special attention should be paid to the risk/benefit ratio at the individual level</td>
</tr>
<tr>
<td>Nuffield Council(^{9})</td>
<td>There must be an appropriate research design to answer the research question</td>
<td>Sustainability and affordability of the standard of care used need to be considered</td>
<td>Minimum should be the standard of care country endeavours to provide nationally</td>
</tr>
</tbody>
</table>

CIOMS, Council for International Organization of Medical Sciences; EGE, European Group on Ethics in Science and New Technologies; NBAC, National Bioethics Advisory Commission; UNAIDS, United Nations Programme on HIV/AIDS.
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